FORMULATION AND EVALUATION OF BISACODYL ENTERIC COATED TABLETS

Dissertation submitted to

The Tamil nadu Dr.M.G.R Medical University, Chennai, Tamil Nadu

In partial fulfillment of the requirements for the award of degree of

MASTER OF PHARMACY

IN

PHARMACEUTICS

Submitted by

(Reg. No. 261210002)

UNDER THE GUIDANCE OF

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Approved by Pharmacy Council of India, New Delhi, and
All India Council for Technical Education. New Delhi.

CERTIFICATE

This is to certify that the dissertation work entitled, **" FORMULATION AND EVALUATION OF BISACODYL ENTERIC COATED TABLETS"** submitted to The Tamil Nadu Dr.M.G.R Medical University, Chennai-32 for the award of the degree of **" MASTER OF PHARMACY IN PHARMACEUTICS"** is a bonafide research work done by **Register No: 261210002** under the supervision and guidance of **Mrs. Priyanka sinha, M.Pharm., Assistant professor,** Department of pharmaceutics, C.L Baid Metha college of pharmacy, Chennai-97, during the academic year 2013-2014.

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ABBREVIATIONS

BP	British pharmacopoeia
USP	United states of pharmacopoeia
JP	Japanese pharmacopoeia
PK	Pharmacokinetics
PD	Pharmacodynamics
HCL	Hydrochloric acid
GIT	Gastrointestinal tract
API	Active pharmaceutical ingredient
GMP	Good manufacturing practice
CAP	Cellulose acetate phthalate
CAT	Cellulose acetate trimelliate
HPMCP	Hydroxy propyl methyl cellulose phthalate
MAE	Methyl acrylic acid co-ethyl acrylate
PEG	Poly ethylene glycol
PG	Propylene glycol
SLS	Sodium lauryl sulphate
HPLC	High performance liquid chromatography
TEC	Triethyl citrate
FT-IR	Fourier transformer infrared spectrophotometer

NOMENCLATURE

%	Percentage
min	Minutes
^{o}C	Degree celusis
RH	Relative humidity
T_g	Glass transition temperature
cps	Centipoise second
mg	Milligram
ml	Millilitre
cm^3	Centimeter cube
w/w	Weight by weight
w/v	Weight by volume
mm	Millimetre
rpm	Revolution per minute
kg	Kilogram
nm	Nanometer
SD	Standard deviation
sec	Seconds

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Last but not least, I thank the GOD who gave me strength, confidence and capacity to bring my dream into reality

Thank You…!

Reg .No: 261210002

DECLARATION

I do here by declare that the thesis entitled, " FORMULATION AND EVALUATION OF BISACODYL ENTERIC- COATED TABLETS" was carried out by me under the guidance and supervision of ***Mrs. Priyanka sinha, M.Pharm, Assistant professor, Department of pharmaceutics, C.L. Baid Metha college of pharmacy, Chennai-97.*** The work embodied in this thesis work is original and is not submitted in any part or full by any other degree of this or any other university**.**

Place: Chennai

Date: [S. ARUN VENKATESH]

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1. INTRODUCTION[1, 32]

Drugs are rarely administered as pure chemical substances alone and are almost always given as formulated preparations or medicines. The development of dosage forms draws on the discipline of biopharmaceutics, which integrates an understanding of formulations, dissolution, stability, and controlled release (pharmaceutics); absorption, distribution, metabolism, and excretion (pharmacokinetics, PK); concentration-effect relationships and drug-receptor interactions (pharmacodynamics, PD); and treatment of the disease state (therapeutics). Drug is the substance used to cure, treat, restore the health state, or optimize a malfunction. Formulation of a dosage form typically involves combining an active ingredient and one or more excipients; the resultant dosage form determines the route of administration and the clinical efficacy and safety of the drug. Optimization of drug doses is also critical to achieving clinical efficacy and safety.

Various aspects of the drug converted into dosage forms:[26]

Transformation of drug into different dosage forms is done for the following reasons:

1. To protect the drug from oxidation (e.g. Vitamin C, Ferrous sulfate), hydrolysis (aspirin) and reduction. e.g. coated tablets, sealed ampoules.
2. To protect the drug from destructive effect of gastric juice (HCL) of the stomach after oral administration e.g. enteric coated tablets.
3. To provide a safe and convenient delivery of accurate dosage.
4. To conceal the bitter (e.g. chloramphenicol), salty or obnoxious taste or odour of a drug substance e.g. capsules, coated tablets and flavoured syrups etc.
5. To provide for the optimum drug action through inhalation therapy. e.g. inhalation aerosols and inhalants.
6. To provide for the drug into one of the body-cavities e.g. rectal suppositories.
7. To provide for the maximum drug action from topical administration sites. e.g. creams, ointments, ophthalmic preparations and E.N.T. (ear, nose and throat) preparation.
8. To provide sustained release action through controlled release mechanism. e.g sustained release tablets, capsules and suspensions.
9. To provide liquid dosage form of the drugs soluble in a suitable vehicle e.g. solutions.

CLASSIFICATION OF DOSAGE FORMS:[26]

The general classification of dosage forms are:

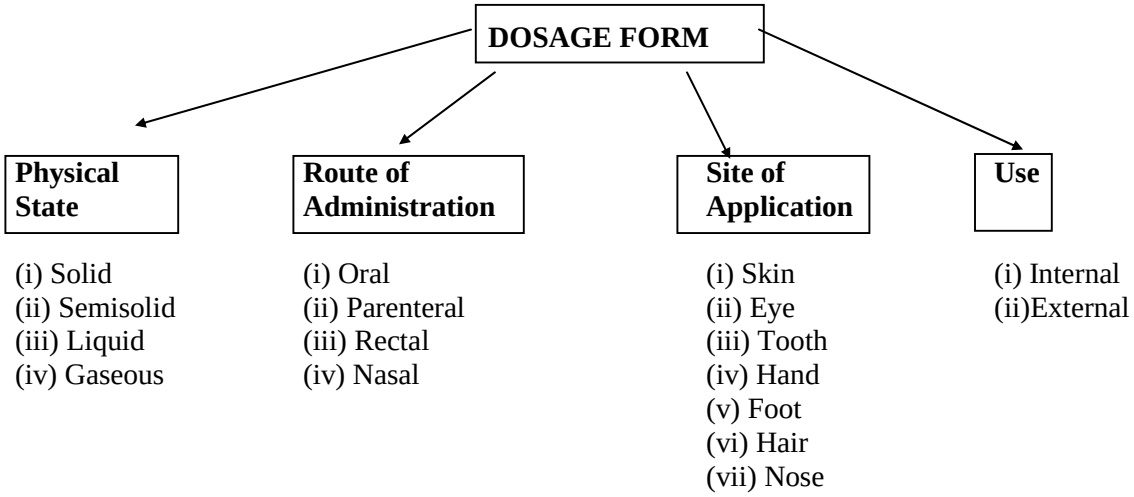


Table No: 1

Classification according to route of administration

Route of administration	Dosage forms
Oral	Powders, tablets, capsules, solutions, emulsions, syrups, elixirs, magmas, gels, cachets, pills.
Parenteral	Solutions, suspensions, emulsions.
Transdermal	Ointments, creams, powders, pastes, lotions, plaster
Rectal	Suppositories, tablets, ointments, creams, douches, foams.
Urethral	Suppositories
Sublingual	Lozenges, tablets
Intranasal	Solutions, sprays, inhalations.
Conjunctival	Ointments
Intra-ocular	Solutions
Intra-respiratory	Aerosols

ORAL DOSAGE FORMS:[56]

Oral dosage forms are the most frequently used route of administration among all routes. Oral drug delivery is the most widely utilized route of administration among all the routes that have been explored for systemic delivery of drugs via pharmaceutical products of different dosage form. Oral route is considered most natural, convenient and safe due to its ease of administration, patient acceptance and cost effective manufacturing process .Oral route of drug administration has wide acceptance up to 50 to 60% of total dosage forms. Solid dosage forms are popular and most preferred route due to its advantages. The most popular dosage forms are being tablets.

TABLETS:[20]

Tablet is a pharmaceutical solid dosage form, comprising a mixture of active substances and excipients, usually in powder form, pressed or compacted into a solid. Tablets dosage form is one of a most preferred dosage form all over the world. In other words, pharmaceutical tablets are solid flat or biconvex disc's prepared by compressing a drug or a mixture of drugs, with or without diluents.

A tablet is usually a compressed preparation that contains:

- 5-10% of the drug (active substance)
- 80% of fillers, lubricants, glidants and binders
- 10% of disintegrants and other compounds which ensure easy disintegration, disaggregation and dissolution of the tablet in the stomach or the intestine.

Advantages of tablets:

1. They are unit dosage form and offer the greatest capabilities of all oral dosage form for the greatest dose precision and the least content variability.
2. Cost is lowest of all oral dosage form.
3. Lighter and compact.
4. Easiest and cheapest to package and strip.
5. Easy to swallow with least tendency for hang-up.
6. Suitable for large scale production.

Disadvantages of tablets:

1. Difficult to swallow in case of children and unconscious patients.
2. Drugs with poor wetting, slow dissolution properties, optimum absorption high in GIT may be difficult to formulate or manufacture as tablet that will still provide adequate or full drug bioavailability.
3. Irritant effects on the GI mucosa by some solids.(eg: aspirin)
4. Possibility of bioavailability problems resulting from slow disintegration and dissolution.

TYPES OF TABLETS:

a. Oral tablets for ingestion:

These tablets are meant to be swallowed intact along with a sufficient quantity of potable water. Over 90% of the tablets manufactured today are ingested orally.

The various types of oral tablets for ingestion are:

1. Standard compressed tablets
2. Multiple compressed tablets
   a. Compression coated tablet
   b. Layered tablet
   c. Inlay Tablet
3. Modified release tablet
4. Delayed action tablet
5. Targeted tablet
   a. Floating tablet
   b. Colon targetting tablet
6. Chewable tablet
7. Dispersible tablet

b. Tablets used in the oral cavity:

The tablets under this group are aimed to release API in oral cavity or to provide local action in this region. The tablets under this category avoids first-pass metabolism, nauseatic sensations and gives rapid onset of action. The various types of tablets used in the oral cavity are.

1. Lozenges and troches
2. Sublingual tablet
3. Buccal Tablet
4. Dental cones
5. Mouth dissolving tablet

c. Tablets administered by other routes:

These tablets are administered by other route except for the oral cavity and so the drugs are avoided from passing through gastro intestinal tract. The other types of administered by other routes are.

1. Vaginal tablet
2. Implants

d. Tablets used to prepare solution:

The tablets under this category are required to be dissolved first in water or other solvents before administration or application. This solution may be for ingestion or parenteral application or for topical use depending upon type of medicament used. The various types of tablets used to prepare solution are.

1. Effervescent tablet
2. Hypodermic tablet
3. Soluble tablet

TYPICAL MANUFACTURING PROCESS OF TABLETS:[13]

Traditionally, tablets have been made by granulation, a process that imparts two primary requisites to formulate: compactibility and fluidity. Both wet granulation and dry granulation (slugging and roll compaction) are used. Numerous unit processes are involved in making tablets, including particle size reduction and sizing, blending, granulation, drying, compaction, and (frequently) coating. Various factors associated with these processes can seriously affect content uniformity, bioavailability, or stability.

The three process involved in the manufacturing of tablets are: Wet granulation, Dry granulation, Direct compression.

Table No: 2

Advantages and disadvantages of various methods of processing of tablets

S.No	Process	Advantages	Disadvantages
1.	**Wet Granulation**	a) Increases and improves the uniformity of powder density. b) Improves cohesion during and after compaction. c) Reduces air entrapment.	a) It is an expensive process. b). Loss of material during various stages of processing. c) Stability may be major concern for moisture sensitive or thermoliable drug
2.	**Dry Granulation or slugging**	a) It requires less equipments and space. b) Time consuming and no need to dry the content. c) Slugging may be used for moisture and heat sensitive material.	a) It requires a specialized heavy duty tablet press to form slug. b) The process tends to create more dust than wet granulation, increasing the potential contamination. c) It does not permit uniform colour distribution
3.	**Direct compression**	a) Cost effectiveness, stability, Faster dissolution, Simplified validation.	a) Segregation, Low dilution potential, cost, and lubricant sensitivity

Table No: 3

Steps involved in the manufacturing of tablets

Wet granulation	Dry granulation	Direct compression
1. Milling and mixing of drugs and excipients	1. Milling and mixing of drugs and excipients	1. Milling and mixing of drugs and excipients
2. Preparation of binder solution	2. Compression into slugs or roll compaction	2. Compression of tablet
3. Wet massing by addition of binder solution or granulating solvent	3. Milling and screening of slugs and compacted powder	
4. Screening of wet mass	4. Mixing with lubricant and disintegrant	
5. Drying of the wet granules	5.Compression of tablet	
6. Screening of dry granules		
7. Blending with lubricant and disintegrant.		
8. Compression of tablet		

Manufacturing process:

1- Dispensing: (weighing and measuring)

Dispensing is the first step in any pharmaceutical manufacturing process. Dispensing is one of the most critical steps in pharmaceutical manufacturing; as during this step, the weight of each ingredient in the mixture is determined according to dose.

2- Sizing:

The sizing (size reduction, milling, crushing, grinding, pulverization) is an impotent step (unit operation) involved in the tablet manufacturing. In manufacturing of compressed tablet, the mixing or blending of several solid ingredients of pharmaceuticals is easier and more uniform if the ingredients are approximately of same size. This provides a greater uniformity

of dose. A fine particle size is essential in case of lubricant mixing with granules for its proper function.

3- Powder blending:

The successful mixing of powder is acknowledged to be more difficult unit operation because, unlike the situation with liquid, perfect homogeneity is practically unattainable.

4- Granulation:

Following particle size reduction and blending, the formulation may be granulated, which provides homogeneity of drug distribution in blend.

5- Drying:

Drying is a most important step in the formulation and development of pharmaceutical product. It is important to keep the residual moisture low enough to prevent product deterioration and ensure free flowing properties. The commonly used dryer includes Fluidized bed dryer, Vacuum tray dryer, Microwave dryer, Spray dryer, Freeze dryer, Turbo - tray dryer, Pan dryer, etc.

6- Tablet compression:

After the preparation of granules (in case of wet granulation) or sized slugs (in case of dry granulation) or mixing of ingredients (in case of direct compression), they are compressed to get final product. The compression is done either by single punch machine (stamping press) or by multi station machine (rotary press).

Figure No: 1 Diagrammatic representation of manufacturing process of tablets

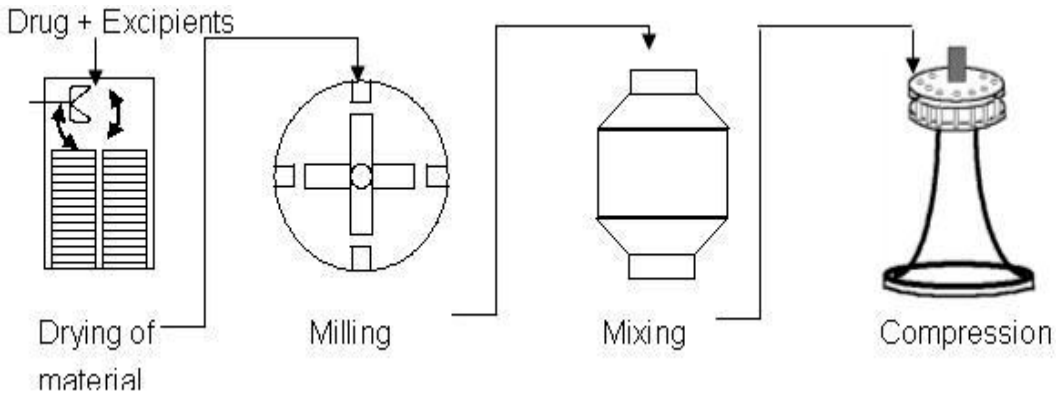
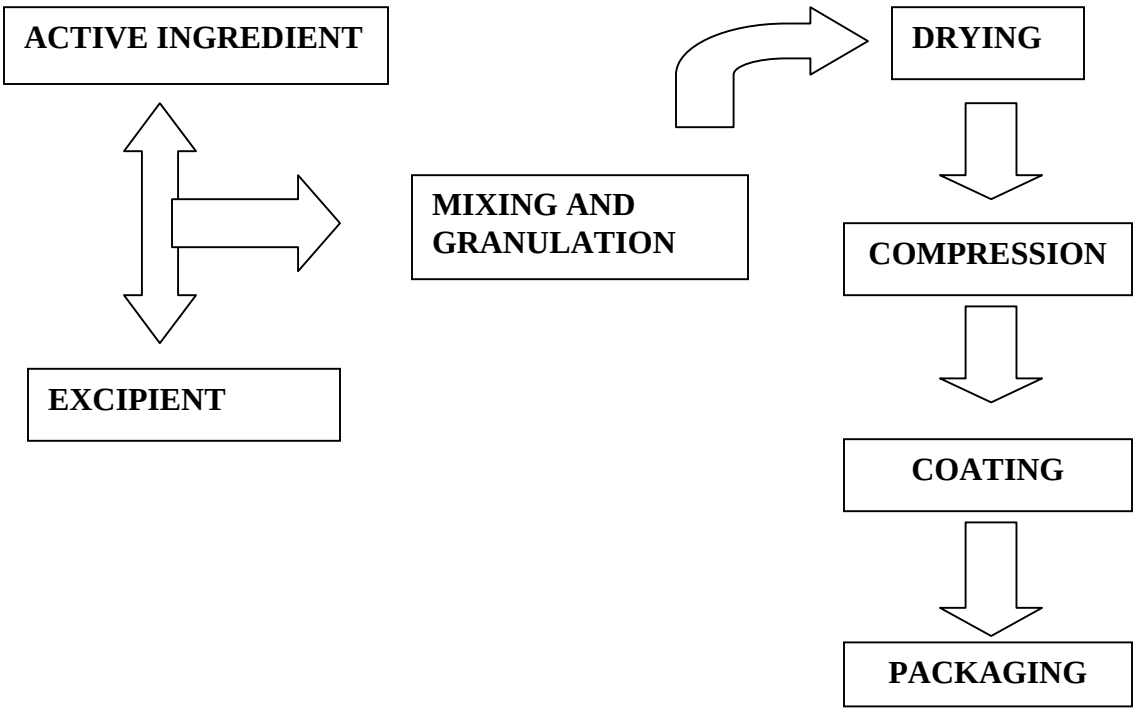


Figure No: 2 Flow chart of the manufacturing process of tablets



TABLET COATING:[2,16]

Tablet coating is a common pharmaceutical technique of applying a thin polymer-based film to a tablet or a granule containing active pharmaceutical ingredients (APIs). Coated tablets are defined as tablets covered with one or more layers of mixture of various substances such as natural or synthetic resins ,gums ,inactive and insoluble filler, sugar, plasticizer, polyhydric alcohol ,waxes ,authorized colouring material and sometimes flavoring material .Coating may also contain active ingredient. Substances used for coating are usually applied as solution or suspension under conditions where vehicle evaporates.

Advantages of tablet coating:

I. Therapy:

a. Avoid irritation of oesophagus and stomach
b. Avoid bad taste
c. Avoid inactivation of drug in the stomach
d. Improve drug effectiveness
e. Prolong dosing interval
f. Improve dosing interval
g. Improve patient compliance

II. Technology:

a. Reduce influence of moisture
b. Avoid dust formation
c. Reduce influence of atmosphere
d. Improve drug stability

Disadvantages of tablet coating:

- Limitations of sugar coating such as relatively high cost, long coating time and high bulk have led to the use of other coating materials.
- However the process of coating is tedious and time-consuming and it requires the expertise of highly skilled technician.

Primary Components Involved In Tablet Coating:

The primary components involved in tablet coating are.

1. Tablet properties
2. Coating process, design and control
3. Coating equipments
4. Parameters of the coating process
5. Facility and ancillary equipments
6. Automation in coating processes.

COATING PROCESS:[2,16]

The coating may be formed by a single application or may be built up in layers through the use of multiple spraying cycles. Rotating coating pans are often used for coating. Uncoated tablets are placed in the pan and the liquid coating solution is introduced into the pan while the tablets are tumbling. The liquid portion of the coating solution is then evaporated by passing air over the surface of the tumbling tablets.

The coating process is usually a batch operating task consisting of the following phases:

a. Identification of batch and Recipe selection (film or sugar coating)

b. Loading/Dispensing (accurate dosing of all required raw materials)

c. Warming

d. Spraying (Both application and rolling are carried out simultaneously)

e. Drying

f. Cooling

g. Unloading

Types of coating process:

Generally , There are three methods used for tablet coating are.

1. SUGAR COATING
2. FILM COATING
3. ENTERIC COATING

1- SUGAR COATING:

Compressed tablets may be coated with coloured or uncoloured sugar layer 30-50% size also multi stage process

2- FILM COATING:

It is deposition of a thin film of polymer surrounding the tablet core (spray). Film coating is more favored over sugar coating 2-3 % over all size, single stage process.

Table No: 4

COMPARISION BETWEEN FILM COATING AND SUGAR COATING

TYPE	FEATURES	FILM COATING	SUGAR COATING
Tablet	Appearance	Retain contour of original core	Rounded with high degree of polish
	Weight increase because of coating material	2 to 3%	30 to 50%
	Logo or 'break lines'	Possible	Not possible
Process	Operator training required	Automation and easy training of operator	Considerable
	Adaptability to GMP	High	Difficulty may arise
	Process stages	Simple stage	Multistage process
	Functional coatings	For controlled release products	Possible apart from enteric coating

ENTERIC COATING:[16,25]

The word "enteric" indicates small intestine therefore enteric coatings prevent release of medication before it reaches the small intestine. The enteric coated polymers remain unionise at low pH, and therefore remain insoluble. But as the pH increases in the GIT, the acidic functional groups are capable of ionisation, and the polymer swells or becomes soluble in the intestinal fluid. Materials used for enteric coatings include CAP, CAT, PVAP and HPMCP, fatty acids, waxes, shellac, plastics and plant fibers.

Definition:

An enteric coating is a barrier that controls the location of oral medication in the digestive system where it is absorbed

Reasons for performing enteric coating:

The possible reasons are.

a. Protection of active pharmaceutical ingredients, from the acidic environment of the stomach. (e.g. enzymes and certain antibiotics)
b. To prevent gastric distress or nausea from a drug due to irritation. (e.g. sodium salicylate)

c. For the delivery of drugs that are optimally absorbed in the small intestine to their primary absorption site in their most concentrated form.
d. To provide a delayed-release component for repeat action.
e. Required for minimizing first pass metabolism of drugs

ENTERIC POLYMERS:[17,18]

Enteric polymers are designed to resist the acidic nature of the stomach contents, yet dissolve readily in the duodenum. The mechanism by which enteric coating polymers function is by a variable pH solubility profile where the polymer remains intact at a low pH but at a higher pH will undergo dissolution to permit the release of the contents of the dosage form.

Mechanism of drug release from enteric coating:

All enteric polymers posses ionizable acid groups, usually a free carboxylic acid from a phthalyl moiety. The equilibrium between unionized insoluble polymer and ionized soluble polymer will be determined by the pH of the medium and the pKa of the polymer. The Henderson-Hasselbach equation can be used to predict the ratio of ionized to unionized polymer based on these two parameters,

i.e.

$$pH - pK_a = \log \frac{[\text{Concentration ionized form}]}{[\text{Concentration unionized form}]}$$

Factors to be considered while selecting enteric polymer:

1. Polymer backbone and pKa
2. Plasticizers and opacifiers
3. Quantity/thickness of the enteric coating
4. Effect of film stability on enteric behavior of formulation
5. Coating process.

Ideal properties of enteric coating material:

a. Resistance to gastric fluids
b. Susceptible/permeable to intestinal fluid
c. Compatibility with most coating solution components and the drug substrate
d. Formation of continuous film
e. Nontoxic, cheap and ease of application
f. Ability to be readily printed

ENTERIC COATING POLYMERS:

The various enteric coating polymers and their dissolution pH are as follows.

- Cellulose acetate phthalate
- Polyvinyl acetate phthalate
- Shellac
- Methacrylic acid copolymers
- Cellulose acetate trimellitate
- Hydroxypropyl methylcellulose phthalate

Table No: 5

Different polymers and their dissolution pH

Polymers	Dissolution pH
Shellac	7.0
Cellulose acetate phthalate (CAP)	6.2
Methacrylic acid copolymers	5.5-7.0
Cellulose acetate trimellitate (CAT)	5.0
Polyvinyl acetate phthalate (PVAP)	5.0
Hydroxypropyl methylcellulose phthalate (HPMCP)	4.5-5.5

New materials used for tablet coating:

The various new materials used for tablet coating are.

a. Zein
b. Aqua-Zein, which is an aqueous zein formulation containing no alcohol.
c. Amylose starch and starch derivatives
d. Dextrins

TABLET DEFECTS:[31]

Tablet defects can come from any of the unit operation upstream and from the tablet press. The raw materials may be of poor quality or do not meet specification, causing excessive fines that lead to a host of defects. Tablet processing problems can be due to the problem in the formulation or in the compression equipment, or both of them. The various defects are.

I. Defects related to tabletting process:

a. **Capping:** It is partial or complete separation of the top or bottom of tablet due air-entrapment in the granular material.
b. **Lamination:** It is separation of tablet into two or more layers due to air-entrapment in the granular material.
c. **Cracking:** It is due to rapid expansion of tablets when deep concave punches are used

II. Defects related to excipients:

a. **Chipping:** It is due to very dry granules.
b. **Sticking:** It is the adhesion of granulation material to the die wall.
c. **Picking:** It is the removal of material from the surface of tablet and its adherence to the face of punch.
d. **Binding:** The problems of chipping, sticking and picking are due to the amount of binder in the granules or wet granules.

III. Defects related to more the one factor:

a. **Mottling:** Due to a colored drug, which has different color than the rest of the granular material, or improper mixing of granular material, or oil spots by using oily lubricant.

IV. Defects related to machine:

a. **Double Impression:** It is due to free rotation of the punches, which have some engraving on the punch faces.

V. Defects related to coating:

a. **Blistering:** It is local detachment of film from the substrate forming blister.
b. **Picking:** It is defect where isolated areas of film are pulled away from the surface when the tablet sticks together and then apart.
c. **Pitting:** It is defect whereby pits occur in the surface of a tablet core without any visible disruption of the film coating.
d. **Blooming**: It is defect where coating becomes dull immediately or after prolonged storage at higher temperatures.
e. **Blushing:** It is defect best described as whitish specks or haziness in the film.
f. **Orange Peel/Roughness:** It is surface defect resulting in the film being rough and non-glossy. Appearance is similar to that of an orange.
g. **Bridging:** This occurs when the coating fills in the lettering or logo on the tablet and is typically caused by improper application of the solution, poor design of the tablet embossing and improper atomization pressure.

DISEASE PROFILE:

Constipation:[6]

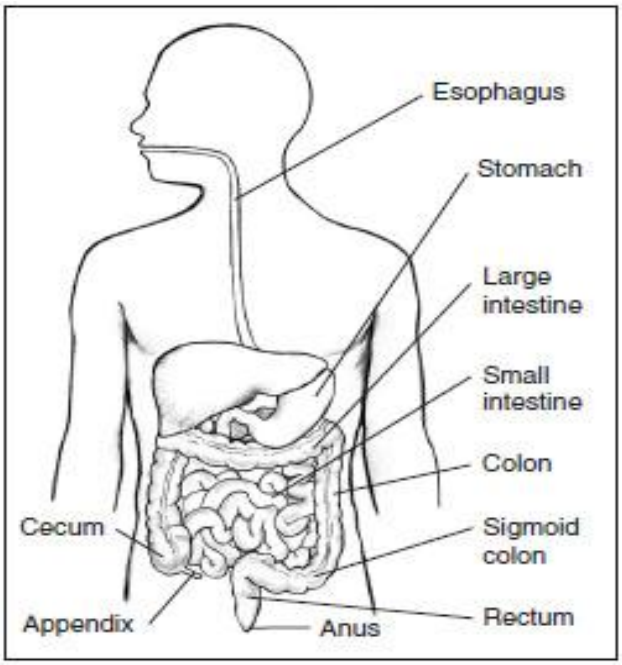
Constipation (also known as **costiveness** or **dyschezia**) refers to bowel movements that are infrequent or hard to pass. Constipation is a common cause of painful defecation. Constipation can be acute, which means sudden and lasting a short time, or chronic, which means lasting a long time, even years. Most constipation is acute and not dangerous.

Gastrointestinal (GI) tract:[7]

The GI tract is a series of hollow organs joined in a long, twisting tube from the mouth to the anus. The movement of muscles in the GI tract, along with the release of hormones and enzymes, allows for the digestion of food. Organs that make up the GI tract are the mouth, esophagus, stomach, small intestine, large intestine which includes the appendix, cecum, colon, and rectum and anus. The intestines are sometimes called the bowel. The last part of the GI tract called the lower GI tract which consists of the large intestine and anus.

Figure No: 3

The lower Gastro intestinal tract



The large intestine absorbs water and any remaining nutrients from partially digested food passed from the small intestine. The large intestine then changes waste from liquid to stool. Stool passes from the colon to the rectum. The rectum is located between the last part of the colon called the sigmoid colon and the anus. The rectum stores stool prior to a bowel movement. During a bowel movement, stool moves from the rectum to the anus, the opening through which stool leaves the body.

Bowel Control Work:[7]

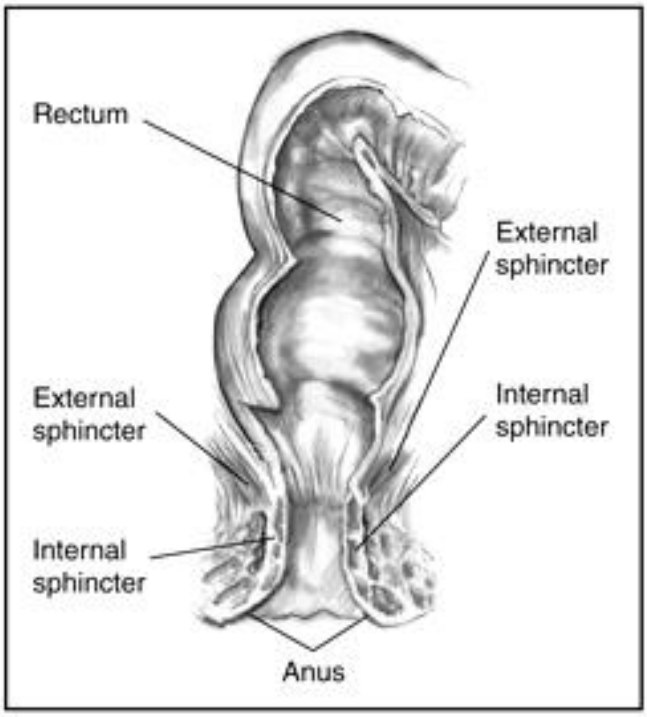
Bowel control relies on muscles and nerves of the rectum and anus working together to

- Hold stool in the rectum
- Let a person know when the rectum is full
- Release stool when the person is ready

Circular muscles called sphincters close tightly like rubber bands around the anus until stool is ready to be released. Pelvic floor muscles also help with bowel control.

Figure No: 4

The external and internal anal sphincter muscles



Causes For Constipation:

Common causes that lead to constipation are.

• Diets Low in Fiber:

Fiber is a substance in foods that comes from plants. Fiber helps stool stay soft so it moves smoothly through the colon. Liquids such as water and juice help fiber to be more effective.

• Medications:

Drugs like narcotics, calcium channel blockers, iron supplements, antidepressants, antacids induces constipation.

• Life changes or daily routine changes:

During pregnancy, women may be constipated due to hormonal changes or due to uterus compresses the intestine. Aging can affect bowel regularity.

• Neurological and metabolic disorders:

Disorders like diabetes and hypothyroidism, disrupt the process the body uses to get energy from food and spinal cord injury, parkinsonism, affect the brain and spine.

• GI tract problems:

Some problems in the GI tract can compress or narrow the colon and rectum, causing constipation. These problems include adhesions, diverticulosis, colon polyps, tumours, celiac disease.

Symptoms:

Symptoms of constipation can include:

a. Infrequent bowel movements and/or difficulty having bowel movements
b. Swollen abdomen or abdominal pain
c. Pain
d. Vomiting

Diagnosis:

The diagnosis for constipation includes.

a. Medical history

b. Physical examination

c. Diagnostic tests:

- Blood test
- Lower GI series
- Flexible sigmoidoscopy or colonoscopy
- Colorectal transit studies
- Anorectal function tests
- Defecography

Treatment:

Treatment for constipation depends on the cause, severity, and duration of the constipation and may include one or more of the following:

a. Changes in eating, diet, and nutrition
b. Exercise and lifestyle changes
c. Medication
d. Surgery

First-line treatments for constipation include changes in eating, diet, and nutrition; exercise and lifestyle changes; and laxatives.

a) Changes in eating, diet, and nutrition:

The Academy of Nutrition and Dietetics recommends consuming 20 to 35 grams of fiber a day for adults.

b) Exercise and lifestyle changes:

Engaging in daily exercise can help people with constipation. Another strategy is to try to have a bowel movement at the same time each day. The best time is 15 to 45 minutes after breakfast because eating helps stimulate the colon.

c) Medication:

Medications like laxatives and enemas are recommended those people who have not treated in diet and life style changes.

NEUROGENIC BOWEL DYSFUNCTION:[8,27]

Neurogenic bowel dysfunction is the term used to describe dysfunction of the colon due to loss of normal sensory and/or motor control or both as a result of central neurological disease or damage. It leads to constipation, faecal incontinence and disordered defaecation.

Etiology:

It is common in spinal cord injury (SCI), brain injury, stroke, spina bifida, amyotrophic lateral sclerosis, multiple sclerosis, sacral nerve injuries and diabetes mellitus, among others.

Causes:

The digestion process is partly managed by messages sent between the brain and digestive system. These messages are sent through nerves. When these nerves are damaged, messages between the brain and digestive system are blocked. This prevents the bowels from working properly. The spinal cord runs from the base of the brain to the lower back. There are two main types of neurogenic bowel, depending on where along the spinal cord the damage occurs.

Reflexic bowel:

This happens when there is damage around the neck or chest. Messages between the colon (large intestine) and the brain are interrupted. As a result, a person may not feel the need to have a bowel movement. However, stool is still building up in the rectum. The build-up triggers a reflex causing the rectum and colon to react, leading to a bowel movement without warning.

Areflexic bowel:

This happens when there is damage around the lower end of the spinal cord. When these lower nerves are damaged, a person is unable to feel when he needs to have a bowel movement. Also, the reflex may be reduced, so the rectum has a difficult time emptying stool. This can lead to constipation.

Symptoms:

The symptoms for the neurogenic bowel dysfunction may includes.

- Swollen abdomen
- Trouble having a bowel movement
- Abdominal pain
- Feeling full (not hungry) quickly
- Repeated bowel accidents
- Bleeding from the rectum

Treatment:

The treatment for the neurogenic bowel dysfunction may includes.

a. Bowel program

b. Medication:

1. Stool softeners: eg. Dioctyl.
2. Colonic stimulants: eg. Senna, Bisacodyl.
3. Osmotic laxatives: eg. Polyethylene glycol, Lactulose.
4. Bulk formers: eg. Ispaghula husk

c. Digital stimulation: Digital stimulation is done to encourage movement of the bowels by stimulating the rectum.

d. Surgery: eg. Colostomy, Ileostomy.

LAXATIVES:[14]

Laxatives are agents which promote bowel evacuation. They may be misused and overused. In excess, they may cause diarrhoea, dehydration, hypokalaemia, atonic bowel and weight loss. Their use may be appropriate in certain situations e.g.

- If there is no response to dietary and lifestyle advice after approximately one month.
- If faecal impaction is present.
- If constipation or painful defaecation is associated with illness, post-surgery or during pregnancy.
- In drug-induced constipation.
- If a patient has a pre-existing condition in which bowel strain is undesirable. e.g. Coronary heart disease.

Mechanism of action of laxatives:

Laxatives generally have been thought to act in one of the following ways.

1. Retention of intraluminal fluid, by hydrophillic or osmotic mechanism.
2. Decreased net absorption of fluid, by effects on small and large bowel fluid and electrolyte transport.
3. Effects on motility by either inhibiting segmenting (non-propulsive) contractions or stimulating propulsive contraction.

Classification of agents used for constipation:

1. Luminally active agents:

a. Hydrophillic colloids:

- Site of Action: Small and Large intestine.

- *Bulk forming agents:* Bran, Psyllium, Methyl cellulose, Sterculia.

b. Osmotic agents:

- Non absorbable inorganic salts

c. Stool- wetting agents:

- surfactants and emollients like mineral oil

2. Non Specific stimulants or irritants:

a. *Diphenylmethanes:* Biscodyl

b. *Anthraquinones:* Cascara and senna

c. Castor oil

3. Prokinetic agents:

a. 5-HT_4 receptor agonists

b. Opioid receptor antagonist

4. Faecal Softeners and Lubricants:

- Site of Action: - Small and Large Intestine.

a. Arachis Oil, Dioctyl sodium sulphosuccinate, Glycerine, Liquid Paraffin

Table No: 6

Classification and Comparison of Representative Laxatives

Laxative effect and latency in usual clinical dosage		
SOFTENING OF FEACES	**SOFT OR SEMIFLUID STOOL**	**WATERY EVACUATION**
ONSET OF ACTION		
1 TO 3 DAYS	**6 TO 8 HOURS**	**1 TO 3 HOURS**
Bulk forming laxatives: Bran Psyllium Methylcellulose *Surfactant laxatives:* Docusates Polaxomers Lactulose	*Stimulant laxatives:* Diphenylmethanes: Biscodyl *Anthraquinone derivatives:* Senna Cascara sagrada	*Osmotic laxatives:* Sodium phosphates Magnesium sulphate Magnesim citrate Milk of magnesia *Castor oil*

2. LITERATURE REVIEW

● **Shrivastava Priyanka and Sethi Vandana.,** ***(2013),*** A Review article on: Superdisintegrants. Disintegration plays a major role in improving the drug activity and hence increases the patient compatibility. The therapeutic activity of the formulations is obtained by disintegration followed by dissolution. Disintegrants are the substances that causes the rapid disintegration of the capsules or tablets into smaller particles that dissolves more rapidly than in the absence of the disintegrants. On the other hand super disintegrants, as it name suggests superior to disintegrants are the substances which facilitates or increases the disintegration time even at low level ,typically 1-10% by weight relative to the total weight of the dosage unit. This article comprises of study of superdisintegrants which are being used in the formulation to provide safe and effective drug delivery with improved patient compliance.

● **Philip Butler and Thorsten Cech.,** ***(2013),*** EXCIPIENT UPDATE - Delivering Gastric-Resistant Functionality Via a Colorless Top Coat. Several formulation development challenges exist in the field of gastric-resistant film-coating. The functional polymer, poly(methacrylic acid-co-ethyl acrylate) (MAE), can react with some pharmaceutical actives (eg, omeprazole), and also with excipients (such as pigments or colourants) commonly used in enteric coating formulation development. This work was initiated to investigate the gastric-resistant functionality obtained by applying a clear, two-component MAE coating formulation onto a tablet sub-coated with a pigmented instant-release coating. In a dry state, MAE films inherently forms very brittle, non-tacky films due to its Tg of 113°C. As a result, plasticizers are required for successful coating applications. The hydrophilic and lipophilic plasticizers evaluated in this study reduced the Tg to only about 65-85°C, which is out of the range of acceptable film-coating applications. Therefore, as fully functional MAE-based gastric-resistant film-coatings are routinely formulated and coated at product temperatures of less than 30°C, it's safe to assume that water acts as a plasticizer during the coating process as well.

● **Kotha Renuka et al.,** ***(2013),*** A Technical Review On Tablet Product Development. The formulation of solid oral dosage forms, particularly tablets had undergone rapid change and development over the last several decades due to emergence of pre compression, induced die feeding, high speed and now ultrahigh speed presses, micro processor control of precompression ejection forces as well as upper punch tightness on tablet presses. The present review focuses on the General Considerations used in choosing the Tablet Components, Additives, activities involved in tablet product design and designed experiments that are used to investigate the process or product variables that systematically influence product quality and Validation of tablet products. It concluding that the above mentioned prospects additional research and development and closure cooperation among the industries, universities and the regulatory agencies are essential to define the properties, the scope, and the use of pharmaceutical excipients in the product development approach of Tablets

● **Amit A. Patel et al.,** ***(2012),*** Formulation and evaluation of doxycycline hydrochloride delayed release enteric coated tablets. The present study was undertaken with an aim to formulate doxycycline hydrochloride delayed release tablets. Successful delivery of drugs specifically to the intestine requires the protection of drug from being released in stomach. This drug is universal antibiotic and can be targeted to the specific site of absorption by enteric coating using pH dependant polymers. The present study demonstrates that the doxycycline hydrochloride compression coated tablets could be targeted to intestine using pH dependent polymers. Enteric coating was carried out using different polymers like Eudragit L-30 D-55, hydroxy propyl methylcellulose phthalate, cellulose acetate phthalate and acryl-EZE® to achieve 5% weight gain and 9 % weight gain. This was concluded that formulation containing Eudragit L 30 D 55 remain intact in 0.1 N HCl and dissolve fast in pH 6.8 phosphate buffer.and shows better results compare to the formulation containing hypromellose phthalate and cellulose acetate phthalate.

● **Ahuja Naresh et al.,** ***(2012),*** A review on development of hpmcp based aqueous enteric coating polymer. The advantages of an aqueous-based coating system have been recognized. This is derived from the drawbacks of organic solvents, including pollution, explosion

hazards and solvent toxicity. Especially, there are risks for operators. For these reasons, water based systems are now gradually being applied instead of organic coating systems. The objective of current study is to develop a HPMCP based enteric coating material which satisfy the need of enteric coating and contains the advantages of aqueous coating material.

- **Singh Deep Hussan et al.,** ***(2012),*** A review on recent advances of enteric coating. Enteric coated tablets are solid unit dosage forms which are designed to bypass the stomach and release the drug in small intestine and are meant for oral administration. The word "enteric" indicates small intestine; therefore enteric coatings prevent release of medication before it reaches the small intestine. Most enteric coatings work by presenting a coated surface that is stable at the highly acidic pH found in the stomach, but breaks down rapidly at a less acidic (relatively more basic) pH. Materials used for enteric coatings include CAP, CAT, PVAP and HPMCP, fatty acids, waxes, shellac, plastics and plant fibers. The present review describes enteric coating, their ideal properties, benefits and limitation, various polymers used, their chemical structure, criteria for drug selection and mechanism, methods of manufacturing and evaluation of enteric coated tablets**.**

- **Patel Harshna and Solanki N S.,** ***(2012),*** Gastro Resistant Drug Delivery System: A Review. The best new therapeutic entity in the world is of little value without an appropriate delivery system. The most important role of a drug delivery system is to get the drug ''delivered'' to the site of action in sufficient amount and the appropriate rate; however it must also meet a number of other essential criteria. These include physical and chemical stability, ability to be economically mass produced in a manner that assures the proper amount of drug in each and every dosage unit and in each batch produced and as far as possible patient acceptability. Enteric-coated dosage forms are designed to resist the acidic environment of the stomach and to disintegrate in the higher pH environment of the intestinal fluid. The sub coating and enteric coating of the core tablets was done. Proton pump inhibitors, H2 blockers, some NSAIDs, insulin delivery etc are suitable candidates for developing delayed release dosage forms.

● **Tsung Yueh Tsai et al.,** ***(2011),*** Effect of diluents on the swelling force of the tablet. The swelling force, especially the swelling force development rate, is a very important parameter in studying the effect of a disintegrant in a tablet. However, a tablet also contains diluents in most cases and the effect of diluents on the swelling force has not been studied. In this study two commonly used diluents, microcrystalline cellulose and calcium phosphate dihydrate, were investigated for their effect on the swelling force with or without a superdisintegrant, Polyplasdone XL. It was found that microcrystalline cellulose alone can develop swelling force depending on the compression force of the tablet. When combined with Polyplasdone XL, it can significantly change the swelling force of Poly plasdone XL. Their results reveals that Depending on the nature, the diluent can display the swelling force or not. Di-tab doesn't show any swelling force but Avicel shows varied degrees of swelling force depending on the compression force. Avicel alone shows gradual force development. With Di-tab added a plateau appears quickly.

● **Ajit Patil et al.,** ***(2011),*** Formulation and evaluation of enteric coated tablets for azithromycin dihydrate to reduce the Gastrointestinal tract side effects.Three formulations of core tablets were prepared and one whoshows rapid disintegration (below three minutes) was selected for enteric coating . Enteric coat was employed by usingdifferent polymers such as HPMC-55, Eudragit, Ethyl cellulose in different ratios Combination of HPMC-55 and ethylcellulose (10:1.5) exibited better dissolution ,disintegration, hardness and friability properties .This study concluded that enteric coated tablets of azithromycin dihydrate can be prepared by using combination of polymers studied and we can reduce the GI tract side effects.

● **Nobutomo Ikarashi et al.,** ***(2011),*** The Laxative Effect of Bisacodyl is attributable to decreased aquaporin-3 expression in the colon induced by increased PGE2 secretion from macrophages. This study was to investigate the role of aquaporin3 (AQP3) in the colon in the laxative effect of bisacodyl. After oral administration of bisacodyl to rats, AQP3, macrophages, cyclooxygenase 2 (COX2), and prostaglandin E2 (PGE2) were examined in the colon. Aquaporins are integral membrane proteins from a larger family of major intrinsic proteins (MIP) that form pores in the membrane of biological cells.Genetic defects involving

aquaporin genes have been associated with several human diseases. From the results suggest that bisacodyl may decrease the expression of AQP3 in the colon, which inhibits water transfer from the luminal to the vascular side and leads to a laxative effect.

● **AppaRao. B et al., *(2010),*** Formulation and Evaluation of Aceclofenac Solid Dispersions for Dissolution Rate Enhancement. Aceclofenac is a novel non-steroidal anti-inflammatory drug (NSAID) having anti-inflammatory and analgesic properties, and is widely used in the treatment of rheumatoid arthritis, osteoarthritis, and ankylosing spondylitis. One of the major problems with this drug is its low solubility in biological fluids, which results into poor bioavailability after oral administration. Therefore, solid dispersions (SDs) of Aceclofenac were prepared using lactose, mannitol and urea to increase its aqueous solubility. Aceclofenac SDs was prepared in 9:1, 7:3 and 4:1 ratios of the drug to polymer (by weight). *In vitro* release profiles of all SDs preparations were comparatively evaluated and also studied against pure Aceclofenac. Faster dissolution was exhibited by solid dispersion containing 9:1 ratio of drug: lactose. The increase in dissolution rate of the drug may be due to increase in wettability, hydrophilic nature of the carrier and due to reduction in drug crystallinity.

● **Rupesh S. Kamble et al., *(2010)***, Formulation and Development Of Enteric Coated Dosage Form Using Ketorolac Tromethamine to reduce the side effects while prolonging its action by using controlled release of oral dosage forms is highly desirable. In the present study direct compression method is used for the preparation of fabricated batches and EudragitL100 is used as coating polymer for enteric coating. In vitro release profiles of batches F1-F4 shows that Ketorolac Tro methamine drug:polymer ratio with Guar gum, Xanthan Gum, Ethyl cellulose and Sodium alginate give 79.32%, 91.52%, 88.35% and 92.19% drug release respectively in 12 hours. *In vitro* release profile of batches F5-F8 shows 85.21%, 95.52%, 93.50%, 97.24% respectively in 12 hours. *In vitro* release profile of batches F9-F12 shows that Ketorolac Tromethamine in ratio 1:3 with Guar gum, Xanthan Gum, Ethylcellulose and Sodium alginate gives release of 89.50%, 98.25%, 95.22%, 100.27% respectively in 12hours. And then showed higher increase in phosphate buffer of pH 6.0 up to 12 hours. All these batches follow near zero order kinetics. This indicates

that the Guar Gum, Xanthan Gum and Ethyl cellulose and Sodium alginate at minimum concentration is not only able to sustain but also control the drug release.

● **Gushit, J. S et al .,** ***(2010),*** **O**verview of the Availability and Utilization of Kaolin as a Potential Raw Material in Chemicals & Drugs Formulation in Nigeria. This work reviewing the potentials of Kaolin as an essential natural occurring mineral raw material employed in the formulation of chemicals, drugs and other medicinal applications. This work is mainly intended for exposing the researchers, chemists, pharmacists and pharmaceutical industries to the availability of kaolin and benefits that could be derived from optimally utilizing same in chemicals and drugs formulation as against the practice of importing the processed kaolin for such purposes. From the study, the properties of kaolin indicates that the hydrophilic surface of kaolin allows it to be easily dispersed in water at neutral pH of 6-8. The most preferred kaolin for pharmaceutical formulations is the finely divided particles because they yield a very large surface area that adsorbs a wide variety of compounds.

● **Tansel Comoglu.,** ***(2010),*** Effects Of Compression Speed And Lubrication On The Compaction Properties Of Some Commonly Used Direct Compression Materials. This study was to investigate the effects of punch speed and lubrication (with and without the addition of 1% magnesium stearate) on the compaction properties of three different classes of excipients; microcrystalline cellulose (Avicel PH 101), pregelatinized starch (Starch 1500) and dibasic calcium phosphate (Fujicalin) having plastic, elastic and brittle fragmentation characteristics were evaluated. The three different speeds were investigated 10, 50 and 100 mm/sec. From the data observed, plastic materials like Avicel PH 101 form harder tablets at low compression speeds whereas brittle fragmenting materials like Fujicalin were relatively unaffected by compaction speed. Avicel PH 101 gave the hardest tablets at all compression speeds with and without the addition of lubricant. It is concluded that because of its plastic deformation under pressure, Avicel PH 101 perform as a binder whereas both fragmentation and plastic deformation take place in Starch 1500.

● **V. P. Pandey et al,.** ***(2009),*** Studies On Diluents For Formulation Of Tablets. Tablet remains popular as a dosage form because of the advantages afforded both to the manufacturer (e.g. Simplicity and economy of preparation, stability and convenience in packing, shipping, and dispensing) and the patient (accuracy of dose, compactness, baldness of taste and ease of administration). Tablet formulation may contain diluent to provide better tablet properties such as improved cohesion, direct compression manufacturing and to promote flow properties. In this study, lactose monohydrate, dibasic calcium phosphate (DCP) and microcrystalline cellulose phosphate (MCCP) were studied as diluents in the same quantity for manufacture of chloroquine phosphate tablet using polyvinyl pyrrolidone K-30 (PVP K-30) as binding agent and sodium starch glycolate (S.S.G.) as disintegrating agent. It was concluded that formualtion containing lactose monohydrate as diluent produces 87.12% drug release in 45 minutes. So lactose monohydrate is considered as suitable diluent for formulating this drug.

● **Amitava Roy et al.,** ***(2009),*** Effects of plasticizers and surfactants on the film forming properties of hydroxypropyl methylcellulose for the coating of diclofenac sodium tablets. In this work, hydroxy propyl methyl cellulose (HPMC) 5cPs, an aqueous soluble polymer was employed for coating diclofenac sodium (DFS) tablets 25 mg for protecting the integrity of the drug yet rendering the drug to release at a faster rate on contact with the gastric environment. The defect free selected formulations were further subjected for studying the effects of surfactants like sodium lauryl sulphate (SLS) and Tween-80 along with the plasticizers. The quality of the aqueous film coats or the plasticizer efficiency in case of PEG-400 is in the order 1.5> 0.5> 1.0% and for PG 1 > 4 > 3% which can be stated on the basis of less incidence of major coat defects like chipping, cracking, orange peel, roughness, blistering, blooming, picking. The quality of aqueous film coat or the surfactant efficiency in case of SLS + PEG-400 is in the order 0.3< 0.5< 0.1% and SLS + PG is in the order 0.5< 0.1< 0.3%. In case of Tween-80 +PEG-400 the order is 0.3 <0.5 < 0.1% and Tween-80 + PG is in the order 0.3< 0.1< 0.5%. They concluding that tablet coating films made of HPMC 5cPs with the addition of PEG at 1.5% and SLS at 0.3% and films made of

HPMC 5cPs with PG at 1% and Tween-80 at 0.3% could be considered as an elegant film forming formulation for solving different coating problems.

● **Rajnikant C.Patel.,** ***(2009),*** Formulation Strategies For Improving Drug Solubility Using Solid Dispersions. The solubility is the biggest challenging aspects for most of the drugs in develpoing the tablets. Solid dispersions have been employed to enhance the dissolution rates of poorly water - soluble drugs. This work is based on the various solubility enhancement strategies in solid dispersion. The approaches described are fusion (melting), solvent evaporation, lyophilization (freeze drying), melt agglomeration process, extruding method, spray drying technology, use of surfactant, electro static spinning method and super critical fluid technology and also highlights the potential applications and limitations of these approaches. They concludes solid dispersion method is one of the effective approaches to achieve the goal of solubility enhancement of poorly water-soluble drugs.

● **T .S. Allagh et al.,** ***(2008),*** Drug distribution in granules: effect of diluent and granule size on the distribution of a hydrophilic low dose drug in granules. Granules of salbutamol sulphate, a hydrophilic drug were prepared using three diluents: Maize starch, lactose and a 50:50 binary mixture of maize starch and lactose to represent insoluble, soluble and sparingly soluble diluents respectively. Granules were prepared using wet granulation by massing and screening with 5%w/v gelatin solution as binder. The dried granules were subjected to sieve analysis and the concentrations of drug in the various granule sizes were determined. Both diluent type and granule size affected drug distribution in the granules with the soluble diluent giving the highest concentration of drug in the larger granules while the insoluble and the sparingly soluble diluents produced granules highest concentration of drugs in the intermediate sized granules. Generally, the sparingly soluble diluent ensured a more even distribution of hydrophilic drugs throughout the granule mass. It concludes that soluble diluents produced highest concentration of hydrophilic drug in larger sized granules and lowest concentrations in the finer granules whereas insoluble and sparingly soluble diluents produced granules with the highest concentration of drug in the intermediate sized granules. Generally, the use of lactose and starch together as diluents produced more uniform distribution of a hydrophilic drug in the various granule sizes.

● **Nighat Razvi et al.,** ***(2005),*** The Effect Of Surfactant On The Dissolution Rate Of Ibuprofen Tablets. The present study was conducted on the effect of surfactant on the dissolution rate of ibuprofen tablets. The cationic (Cetyl Trimethyl bromide) and anionic (Sodium dodecyl sulphate) surfactant present in the dissolution media have remarkable effect on the dissolution rate of Ibuprofen. From the values observed, SDS at 0.5% concentration in water shows drug release 97.61% in 60 minutes. So it was concluded that maximum dissolution was obtained in the presence of anionic surfactant (Sodium dodecyl sulphate) at 0.5% concentration of deionized water whereas non-ionic (Tween-80) surfactant had little effect on the dissolution of Ibuprofen tablets

● **Quintin Verloop et al., (** ***2004),*** Compounded laxative formulations for substituting phenolphthalein with sennosides A & B in solid dosage forms. This study was undertaken to develop compounded formulations of laxative products containing the stimulant laxatives sennosides A and B for the purpose of carcinogenicity occuring with the phenolphtahlein and subesquent banned in several countries. The method of formulation is direct compression and wet granulation method. Both DSC and HPLC confirmed no incompatibilities in the dry mixtures. It is concluded that compatibility evaluation shows that dry powder mixtures for filling capsules and for direct compression of tablets can thus be used to formulate sennosides A & B into tablets.

● **Kestur Gundappa Satyanarayana et al.,** ***(2004),*** Clay Surfaces- Fundamentals and Applications. In this review, in case of solid dosage excipients clay minerals are classified according to their functionality as excipient in solid dosage forms. Kaolinite is mainly used as a diluent because of its white to greyish-white colour. Its suitability as pharmaceutical excipient greatly depends on the geological nature (sedimentary, residual, and hydrothermal) and mineral composition of the deposits, which have an important effect on texture and particle size distribution, and consequently, on the rheological properties (flow) of the powder mass. It is concluded that kaolin used as an diluent for tablet and capsule formulations particularly for the immediate and modified release tablets dosage forms.

● **Eija Leskinen**., ***(2003),*** Tablet disintegration: Effects of temperature and pH of aqueous disintegrating fluid and influence of solubility of diluent on the behaviour of superdisintegrants. In the experimental work three grades of lactose were combined with foursuperdisintegrants and tablets were prepared with different porosity levels. Also one hygroscopic and insoluble diluent, sorbitol and dicalcium phosphate dihydrate were used in combination with disintegrants. Disintegration and calorimetric measurements were made in three temperatures with water and simulated gastric and intestinal fluid. Investigations show that superdisintegrants have a greater effect on disintegration time in an insoluble system than in a soluble or partially soluble system. It is concluded that results showed that the choice of tablet excipients can have a great influence in disintegration time. As the dissolution of drug is dependent on the disintegration rate of tablet, it is thus important to pay attention to diluent and disintegrant used in order to achieve the desired availability for the drug.

● **European Patent Specification.,** ***(1995),*** Bisacodyl Dosage Form: This subject invention involves pharmaceutical compositions in dosage unit form, for peroral administration of bisacodyl to a human or lower animal having a gastrointestinal tract, with a lumen there through, with a small intestine and a colon with a junction there between, comprising:

(a) a safe and effective amount of rapidly-dissolving bisacodyl means; and

(b) a delivery means which completely surrounds and encases the bisacodyl means in the dosage unit form prior to oral administration and which prevents the release of bisacodyl from the dosage form into the lumen of the gastrointestinal tract during transport of the dosage form through the lumen until the dosage form is near the junction between the small intestine and the colon or in the colon, and which then releases the bisacodyl in the lumen near the junction between the small intestine and the colon or within the colon.

3. AIM AND OBJECTIVE

The aim of the present study is to design and formulate the enteric - coated tablets of bisacodyl and to comply the physio- chemical properties as per BP limits.

- Bisacodyl is an highly acid liable and it is used as stimulant laxative drug that works directly on the colon to produce a bowel movement. It is typically prescribed for relief of constipation and for the management of neurogenic bowel dysfunction as well as part of bowel preparation before medical examinations

To achieve these goal various prototype formulation trails were taken by wet granulation method using different diluents and observing difference in the in-process parameters such as dissolution, assay for complying the data as per BP limits under quality control.

The main objective of this study are:

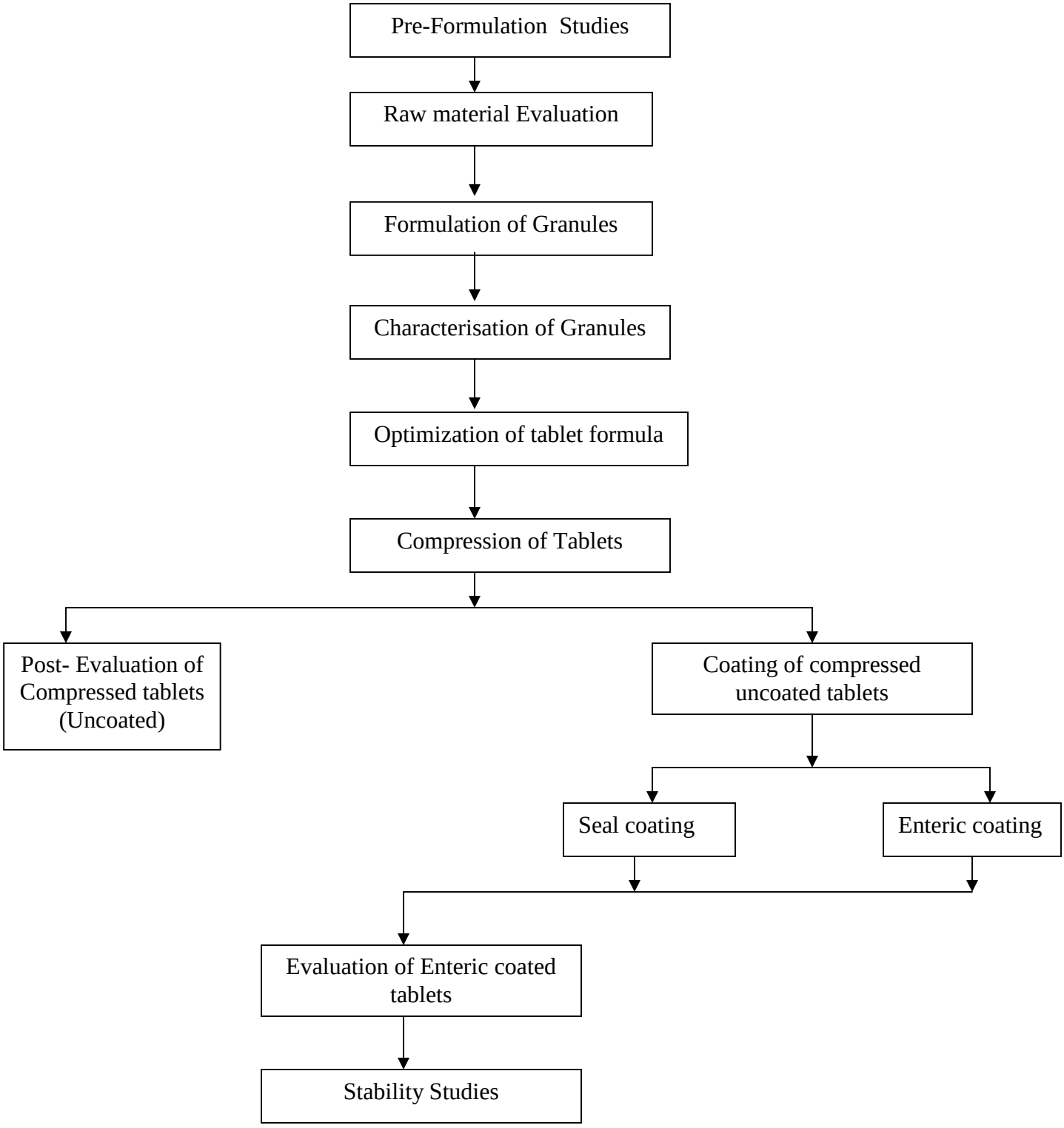
1. To formulate the stable bisacodyl enteric coated tablets. To study the influence on various diluents effects during compression of tablets.
2. To evaluate the formulated tablets and to comply with the BP limits.
3. To study the release profile of the formulated enteric coated tablet and to compare their drug release profile with the innovator product.
4. To perform stability studies for the optimized formulation for three months at $40^0C \pm 2^0C$, 75 % ± 5 % RH.

4. PLAN OF WORK

The present work was carried out to formulate bisacodyl enteric- coated tablets and to evaluate the *in-vitro* dissolution study and stability studies for the prepared bisacodyl enteric- coated tablets It was planned to carry out this study in the sequence below.

1. Literature survey
2. Preformulation studies
    a. Evaluation of API's
        - Physical appearance
        - Solubility
        - Micrometric properties like Bulk density, Tapped density, Compressibility index (%), Hausner's ratio, Particle size distribution, Moisture content.
    b. Drug- excipient compatibility studies.
        - Physical observation.
        - FT- IR studies
3. Formulation of granules by wet granulation method.
4. Evaluation of pre - compression studies for the final blend of all formulations
        - Bulk density, Tapped density, Compressibility index, Hausner's ratio, sieve analysis and moisture content.
5. Compressing the core tablet under 8 station compression machine.
6. Performing the coating process for the core tablet by the pan coating method using enteric- coating polymer.
7. Evaluation of enteric - coated tablets.
        - Hardness, Thickness, Friability, disintegration test, *in vitro* dissolution study, Drug content.
8. To perform stability studies for final optimized formulation.

PLAN OF STUDY



5.1 DRUG PROFILE[34,54]

Drug name: Bisacodyl

Synonym:

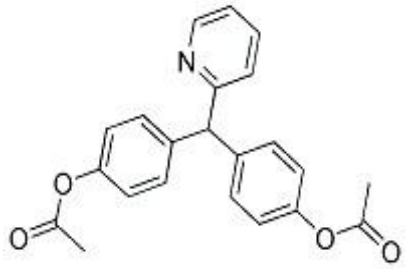
4,4'-(Pyridin-2yl methylene) bis(phenyl acetate), bisacodilo, 4,4'-(2-Pyridylmethylene) bis(phenyl acetate).

Chemical Name: 4,4'-(2-Pyridylmethylene) di(phenylacetate)

Chemical Formula: $C_{22}H_{19}NO_4$

Molecular weight: 361.39

Chemical structure:



Description:

Bisacodyl is a hygroscopic diphenol. Bisacodyl is an over-the-counter stimulant laxative that can be used in either oral or suppository form. Stimulant laxatives encourage bowel movements by increasing the muscle contractions in the intestinal wall that propel the stool mass.

Therapeutic Category : Catharatics and laxatives

PHYSICAL AND CHEMICAL PROPERTIES:

Physical State: White to off-white crystalline powder

Melting Point: 131 – 135^{0}C

Solubility: Soluble in alcohol (slightly), ether (slightly), chloroform, and acetone. Practically insoluble in water.

Uses:

- ♦ It is used as stimulant laxative to relieve occassional constipation.
- ♦ It is used for emptying the bowel prior to surgery or radiological examinations.
- ♦ It is also used for the management of neurogenic bowel dysfunction.

Available forms:

Bisacodyl is usually available as 5mg tablets, 10 mg suppositories, or 5 mg pediatric suppositories. It is also available as a 1.25 US fluid ounces (37 ml) prepackaged enema containing a 10 mg delivered dose of liquid bisacodyl.

Dosage and Administration:

1.Oral:

Indication: Constipation:

Adult: 5-10 mg at night.

Child: >4 yr: 5 mg at night time.

2. Rectal

Adult: 10 mg suppository/enema admin in the morning.

Child: <10 yr: 5 mg in the morning.

3.Oral

Indication: Bowel evacuation.

Adult: Initially, 10-20 mg the night before the procedure followed by 10 mg suppository admin rectally the next morning.

Child: >10 yr: Same as adult dose. 4-10 yr: 5 mg the night before the procedure and 5 mg suppository admin rectally the following morning. .

PHARMACOLOGY:

Mechanism of action:

Bisacodyl acts locally in the gastro intestinal tract by stimulating enteric nerves to cause colonic mass movements. It is also a contact laxative, it increases fluid and NaCl secretion. Action of bisacodyl on small intestine is negligible; stimulant laxatives mainly promote evacuation of the colon.

PHARMACOKINETICS:

a. Absorption:

Absorption of bisacodyl is minimal following oral or rectal administration. The compound bis-(p-hydroxyphenyl)-pyridyl-2-methane (BHPM), is formed in the intestine by hydrolysis of bisacodyl where it gets absorbed into the blood stream, and is conjugated and circulates as the inactive form (mainly as a glucuronide derivative). Onset: Oral therapeutic dosages: evacuation is produced in 6–12 hours. Rectally administered bisacodyl produces evacuation of the colon within 15 minutes to 1 hour.

b. Distribution:

Bisacodyl is distributed into the milk. The plasma protein binding was found to be greater than 99%

c. Metabolism:

Bisacodyl is converted to bis(p-hydroxyphenyl)pyridyl-2-methane by intestinal or bacterial enzymes. It takes place in the liver.

d.Excretion:

Bisacodyl is mainly excreted in urine and faeces as glucoronide.

Table No: 7

Pharmacokinetic parameters of Bisacodyl

Parameters	Data
Bioavailability	15%
Biological half life	16 hours
Metabolism	Hepatic (CYP450-mediated)

Special Populations:

Hepatic Impairment:

No specific dosage recommendations for bisacodyl in hepatic impairment. Minimally absorbed systemically following oral or rectal administration.

Renal Impairment:

No specific dosage recommendations for bisacodyl in renal impairment. Minimally absorbed systemically following oral or rectal administration.

Geriatric Patients:

No specific geriatric dosage recommendations for bisacodyl.

Drug – Drug interactions:

a. Milk or antacids:

   May cause enteric coating of tablets to dissolve, resulting in gastric lining irritation or gastric indigestion. Do not give antacids or milk within one hour of taking the drug (enteric coated).

b. Special precautions for use in children:

   The tablet form of bisacodyl is not recommended for children under 6 years old.

Adverse effects:

The most common side effects for bisacodyl includes

a. GI irritation, fluid and electrolyte loss, or diarrhea.
b. Short-term usage (at normal dosages) typically results in abdominal pain or cramps, faintness, nausea/vomitting and mild abdominal discomfort.
c. Prolonged bisacodyl therapy can cause hypokalemia.

INNOVATOR PRODUCT DETAILS:

Tablet strength: 5mg enteric coated tablet

S.NO	CONTENTS	DESCRIPTION
1.	Brand name	Dulcolax
2.	Label claim	Each enteric coated tablet contains 5mg bisacodyl
3.	Manufacturer	Boehringer Ingelheim
4.	Dosage form	Tablet
5.	Physical parameters: Description Hardness Thickness Average weight	 5mg pale yellow, round, smooth, bicovex shaped tablets. 2 – 3 kg/cm^2 3.31mm 93mg/tab with enteric coating
6.	Shelf life	3years
7.	Storage	Store at room temperature between 25- 30^{0}C
8.	Inactive ingredients	Lactose monohydrate, Maize starch, Soluble maize starch, Glycerol (85%), Magnesium stearate, Sucrose, Talc, Acacia(powdered), Titanium dioxide, Methacrylic acid-methyl methacrylate copolymer (1:1), Methacrylic acid-methyl methacrylate copolymer (1:2), Castor oil, Macrogol 6000, Yellow iron oxide. White bees wax, Carnauba wax, Shellac

5.2 EXCIPIENT PROFILE

DIBASIC CALCIUM PHOSPHATE, DIHYDRATE:[35]

● **Non-proprietary Names:**

BP: Calcium Hydrogen Phosphate

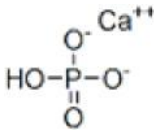
JP: Dibasic Calcium Phosphate Hydrate

● **Synonyms:**

Calcium hydrogen orthophosphate dihydrate, Calcium monohydrogen phosphate dihydrate, Phosphoric acid calcium salt (1 : 1) dihydrate, Secondary calcium phosphate , DI-TAB, Emcompress.

● **Chemical Name:** Dibasic calcium phosphate dihydrate

● **Structural Formula:**



● **Empirical Formula:** $CaHPO_4 .2H_2 0$

● **Molecular Weight:** 172.09

● **Functional Category:** Tablet and capsule diluent.

● **Description:**

Dibasic calcium phosphate dihydrate is a white, odorless, tasteless powder or crystalline solid. It occurs as monoclinic crystals. It is commercially available in two particle size grades that is milled and unmilled or coarser grade materials.

● **Typical properties:**

♦ Density: 2.389 g/cm^3

♦ Acidity/alkalinity: pH = 7.4

♦ Melting point: Dehydrates below 100^0C

♦ **Solubility:**

Practically insoluble in ethanol, ether, and water; soluble in dilute acids.

- **Applications:**

  - It is widely used in tablet formulations both as an excipient and as a source of calcium and phosphorus in nutritional supplements.
  - It is also used in pharmaceutical products because of its compaction properties, and the good flow properties of the coarse grade material.
  - It is abrasive and a lubricant is required for tableting that is 1% w/w of magnesium stearate or 1% w/w of sodium stearyl fumarate is commonly used.
  - It is also used in toothpaste and dentifrice formulations for its abrasive properties.

- **Stability and Storage:**

Dibasic calcium phosphate dihydrate is a non-hygroscopic, relatively stable material. However, under certain conditions the dihydrate can lose water of crystallization. The bulk material should be stored in a well-closed container in a cool, dry place.

- **Incompatibilities:**

  - Dibasic calcium phosphate dihydrate should not be used to formulate tetracycline antibiotics.
  - Dibasic calcium phosphate dihydrate is incompatible with aspartame, ampicillin, indoemethacin, cephalexin, aspirin and erythromycin.

KAOLIN:[36]

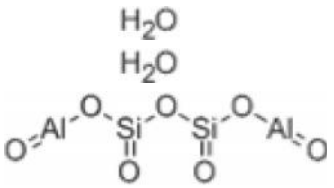
- **Non-proprietary Names:**

BP: Heavy Kaolin
JP: Kaolin

- **Synonyms:**

Kaolinite , China clay, Bolus alba, Porcelain clay, White bole, E559.

- **Chemical Name:** Hydrated aluminum silicate.
- **Structural Formula:**



● **Empirical Formula:** $Al_2H_4O_9Si_2$

● **Molecular Weight:** 258.16

● **Functional Category:**

Adsorbent, suspending agent, tablet and capsule diluent.

● **Description:**

Kaolin occurs as a white to grayish-white colored, unctuous powder free from gritty particles. It has a characteristic earthy or claylike taste, and when moistened with water it becomes darker in color and develops a clay like odor.

● **Typical properties:**

- Acidity/alkalinity: pH = 4.0-7.5
- Hygroscopicity: At relative humidities between about 15–65%, the equilibrium moisture content at 25^0C is about 1% w/w, but at relative humidities above about 75%, kaolin absorbs small amounts of moisture.
- **Solubility:**

  Practically insoluble in diethyl ether, ethanol(95%), water, other organic solvents, cold dilute acids, and solutions of alkali hydroxides.

● **Applications:**

Kaolin is a naturally occurring mineral used in oral and topical pharmaceutical formulations. In oral medicines, kaolin has been used as a diluent in tablet and capsule formulations. It has also been used as a suspending vehicle. Therapeutically, kaolin has been used in oral antidiarrheal preparations.

● **Stability and Storage:**

Kaolin is a stable material. Since it is a naturally occurring material, It may be sterilized by heating at a temperature greater than 160 ^{0}C for not less than 1 hour. It should be stored in a well-closed container in a cool, dry place.

● **Incompatibilities:**

The adsorbent properties of kaolin may influence the absorption of other orally administered drugs. Kaolin is incompatible with drugs amoxicillin, cimetidine, ampicillin, digoxin, lincomycin, phenytoin, warfarin and tetracycline.

STARCH:[37]

● **Non-proprietary Names:**

BP: Maize starch, Potato starch, Rice Starch, Tapioca Starch, Wheat Starch.

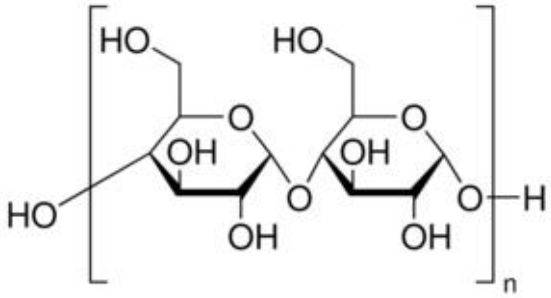
JP: Corn Starch, Potato Starch, Rice Starch, Wheat Starch.

● **Synonyms:**

Amido, amidon, amilo, amylum, maydis amylum, Melojel, oryzae amylum, pisi amylum, solani amylum, tritici amylum.

● **Chemical Name:** Starch

● **Structural Formula:**



● **Empirical Formula and Molecular Weight:**

$(C_6H_{10}O_5)_n$ where n = 300-1000.

● **Functional Category:**

Tablet and capsule diluent, tablet and capsule disintegrant, tablet binder, thickening agent.

● **Description:**

Starch occurs as an odorless and tasteless, fine, white to off-white powder. It consists of very small spherical or ovoid granules or grains whose size and shape are characteristic for each botanical variety.

● **Typical properties:**

- Acidity/alkalinity: pH = 4.0-8.0 for aqueous dispersion.
- Density: 1.478 g/cm^3
- **Moisture content :**

  All starches are hygroscopic and absorb atmospheric moisture to reach the equilibrium humidity. An approximate value of different starches at 50% relative humidity were given, 12% for corn starch, 14% for pea starch, 18% for potato starch, 14% for rice starch, 13% for wheat starch.
- **Solubility:**

  Practically insoluble in cold ethanol (96%) and in cold water. Starch becomes soluble in hot water at temperatures above the gelatinization temperature. Starches are partially soluble in dimethylsulfoxide and dimethylformamide.

● **Applications:**

a. Starch is a versatile excipient used primarily in oral solid-dosage formulations where it is utilized as a binder, diluent, and disintegrant.
b. Starch is used as a diluent for the preparation of standardized triturates of colorants, potent drugs, and herbal extracts, facilitating subsequent mixing or blending processes in manufacturing operations.
c. Starch quantities of 3–10% w/w can act as an anti adherent and lubricant in tabletting and capsule filling.
d. In tablet formulations, freshly prepared starch paste is used at a concentration of 3–20% w/w as a binder for wet granulation.
e. Starch is one of the most commonly used tablet disintegrants at concentrations of 3–25% w/w.

● **Stability and Storage:**

Dry starch is stable if protected from high humidity. Starch is considered to be chemically and microbiologically inert under normal storage conditions. Starch should be stored in an air tight container in a cool, dry place.

● **Incompatibilities:**

Starch is incompatible with strongly oxidizing substances. Colored inclusion compounds are formed with iodine.

MICRO CRYSTALLINE CELLULOSE:[38]

● **Non-proprietary Names:**

BP: Microcrystalline Cellulose
JP: Microcrystalline Cellulose

● **Synonyms:**

Avicel PH, Celex, Cellulose gel, Hellulosum microcristallinum, Emcocel, Ethispheres, Fibrocel, Pharmacel, Vivapur.

● **Chemical Name:** Cellulose.

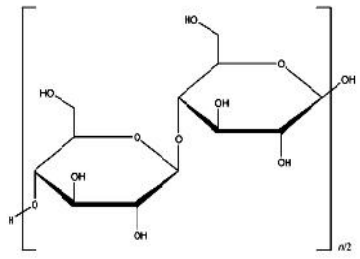
● **Empirical Formula and Molecular Weight:**

$(C_6H_{10}O_5)_n$ where n = 220

● **Functional Category:**

Adsorbent, suspending agent, tablet and capsule diluent, tablet disintegrant.

● **Structural Formula:**



● **Description:**

Microcrystalline cellulose is a purified, partially depolymerized cellulose that occurs as a white, odorless, tasteless, crystalline powder composed of porous particles.

● **Typical properties:**

- Acidity/alkalinity: pH = 5.0 to 7.5
- Density: 1.512 to 1.668 g/cm^3
- Melting point: Chars at 260–270^{0}C
- **Solubility:** Slightly soluble in 5% w/v sodium hydroxide solution. Practically insoluble in water, dilute acids, and most organic solvents.

● **Pharmaceutical applications:**

Microcrystalline cellulose is widely used in pharmaceuticals, primarily as a binder/diluent in oral tablet and capsule formulations where it is used in both wet-granulation and direct-compression processes.

Table No: 8

Uses of Microcrystalline cellulose with concentration in percentage(%)

Use	Concentration (%)
Adsorbent	20-90
Anti adherent	5-20
Capsule binder/diluents	20-90
Tablet disintegrant	5-15
Tablet binder/diluents	20-90

● **Stability and Storage:**

Microcrystalline cellulose is a stable though hygroscopic material. The bulk material should be stored in a well-closed container in a cool, dry place.

● **Incompatibilities:**

Microcrystalline cellulose is incompatible with strong oxidizing agents.

POVIDONE:[39]

● **Non-proprietary Names:**

BP: Povidone

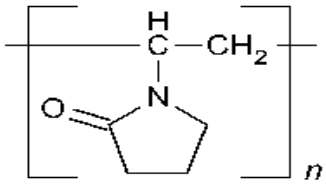
JP: Povidone

● **Synonyms:**

Kollidon, Plasdone, Polyvinyl pyrrolidione, Povidonum, PVP, 1-vinyl-2-pyrrolidinone polymer.

● **Chemical Name:** 1-Ethenyl-2-pyrrolidinone homopolymer

● **Structural Formula:**



● **Empirical Formula:** $(C_6H_9NO)_n$

● **Molecular Weight:** n = 2500–3,00,0000

Table No: 9

Different grades of povidone with approximate molecular weight

S.No	K- value	Approximate Molecular Weight
1.	12	2500
2.	15	8000
3.	17	10000
4.	25	30000
5.	***30***	***50000***
6.	60	400000
7.	90	1000000
8.	120	3000000

● **Functional Category:**

Disintegrant, dissolution enhancer. suspending agent, tablet binder.

● **Description:**

Povidone occurs as a fine, white to creamy-white coloured, odorless or almost odorless, hygroscopic powder.

● **Typical properties:**

- Acidity/alkalinity: pH = 3.0–7.0 (5% w/v aqueous solution)
- Density: 1.180 g/cm^3
- Melting point: Softens at 150^{0}C
- **Moisture content:**

  Povidone is very hygroscopic, significant amounts of moisture being absorbed at low relative humidities.

- **Solubility:**

  Freely soluble in acids, chloroform, ethanol (95%), ketones, methanol, and water. Practically insoluble in ether, hydrocarbons, and mineral oil.

● **Pharmaceutical applications:**

- Povidone is used in a variety of pharmaceutical formulations and also primarily used in solid-dosage forms. Povidone solutions are used as binders in wet granulation process.
- Povidone is used as a suspending, stabilizing, or viscosity-increasing agent in a number of topical and oral suspensions and solutions.

Table No: 10

Uses of Povidone with Concentration in percentage(%)

Use	Concentration(%)
Carrier for drugs	10-25
Dispersing agent	5
Eye drops	2-10
Suspending agent	5
Tablet binder, diluent, or coating agent	0.5-5

● **Stability and Storage:**

Povidone darkens to some extent on heating at 150^0C, with a reduction in aqueous solubility. It is stable to a short cycle of heat exposure around 110–130^0C. Since the powder is hygroscopic, it should be stored in an airtight container in a cool, dry place.

● **Incompatibilities:**

Povidone is compatible in solution with a wide range of inorganic salts, natural and synthetic resins, and other chemicals. It forms molecular adducts in solution with sulfathiazole, sodium salicylate salicylic acid, phenobarbital, tannin, and other compounds.

CROSCARMELLOSE SODIUM:[40]

● **Non-proprietary Names:**

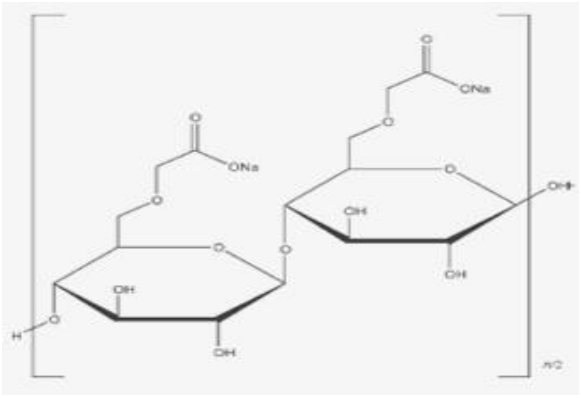
BP: Croscarmellose Sodium
JP: Croscarmellose Sodium

● **Synonyms:**

Ac-Di-Sol, Crosslinked carboxymethylcellulose sodium, Modified cellulose gum, Pharmacel XL, Primellose, Solutab, Vivasol.

● **Chemical Name:** Cellulose, carboxymethyl ether, sodium salt, crosslinked.

● **Structural Formula:**



● **Functional Category:** Tablet and capsule disintegrant.

● **Description:**

Croscarmellose sodium occurs as an odorless, white or greyish white powder.

● **Typical properties:**

- Acidity/alkalinity: pH = 5.0–7.0 in aqueous dispersion.
- Density: 1.543 g/cm^3
- **Solubility:**

  Insoluble in water, although croscarmellose sodium rapidly swells to 4–8 times its original volume on contact with water. Practically insoluble in acetone, ethanol and toluene.

● **Pharmaceutical applications:**

- Croscarmellose sodium is used in oral pharmaceutical formulations as a disintegrant for capsules, tablets and granules.
- Croscarmellose sodium may be used in both direct-compression and wet-granulation processes.
- Croscarmellose sodium at concentrations up to 5% w/w may be used as a tablet disintegrant, although normally 2% w/w is used in tablets prepared by direct compression and 3% w/w in tablets prepared by a wet-granulation process.

Table No: 11

Uses of Croscarmellose sodium with Concentration in Percentage(%)

USE	CONCENTRATION(%)
Disintegrant in capsules	10-25
Disintegrant in tablets	0.5-5.0

● **Stability and Storage:**

Croscarmellose sodium is a stable though hygroscopic material. Croscarmellose sodium should be stored in a well-closed container in a cool, dry place.

● **Incompatibilities:**

Croscarmellose sodium is not compatible with strong acids or with soluble salts of iron and some other metals such as aluminum, mercury, and zinc.

SODIUM LAURYL SULPHATE:[41]

● **Non-proprietary Names:**

BP: Sodium Lauryl Sulphate
JP: Sodium Lauryl Sulfate

● **Synonyms:**

Dodecyl Alcohol Hydrogen Sulfate, Sodium Salt, Dodecylsulfate Sodium Salt, Sodium N-Dodecyl Sulfate, Sodium Laurilsulfate, Sodium Monolauryl Sulfate, SDS, SLS.

● **Chemical Name:** Sulfuric acid monododecyl ester sodium salt (1 : 1)

● **Empirical Formula:** $C_{12}H_{25}NaO_4S$

● **Molecular Weight:** 288.38

● **Functional Category:**

Anionic surfactant, detergent, emulsifying agent, skin penetrant, tablet and capsule lubricant, wetting agent.

● **Description:**

Sodium lauryl sulfate consists of white or cream to pale yellow colored crystals, flakes, or powder having a smooth feel, a soapy, bitter taste, and a faint odor of fatty substances.

- **Typical properties:**

  - Acidity/alkalinity: pH = 7.0–9.5 (1% w/v in aqueous solution)
  - Density: 1.07 g/cm^3
  - Moisture content: Sodium lauryl sulfate is not hygroscopic and its moisture content is ≤ 5%.
  - **Solubility:**

    Freely soluble in water, giving an opalescent solution. Practically insoluble in chloroform and ether.

- **Pharmaceutical applications:**

  - Sodium lauryl sulfate is an anionic surfactant employed in a wide range of non-parenteral pharmaceutical formulations and cosmetics.
  - It is an detergent and wetting agent effective in both alkaline and acidic conditions.
  - In recent years it has found application in analytical electrophoretic techniques: SDS (sodium dodecyl sulfate) polyacrylamide gel electrophoresis is one of the more widely used techniques for the analysis of proteins

- **Safety:**

  - Sodium lauryl sulfate is widely used in cosmetics and oral and topical pharmaceutical formulation.
  - Repeated, prolonged exposure to dilute solutions may cause drying and cracking of the skin; contact dermatitis may develop.
  - Prolonged inhalation of sodium lauryl sulfate will damage the lungs.

- **Incompatibilities:**

Sodium lauryl sulfate reacts with cationic surfactants, causing loss of activity even in concentrations too low to cause precipitation. Sodium lauryl sulfate is incompatible with salts of polyvalent metal ions, such as aluminum, lead, tin or zinc.

COLLOIDAL SILICON DIOXIDE:[42]

● **Non-proprietary Names:**

BP: Colloidal Anhydrous Silica
JP: Light Anhydrous Silicic Acid

● **Synonyms:**

Aerosil, Colloidal silica, Fumed silica, Silica sol, Silicic anhydride, Silicon dioxide fumed, Synthetic amorphous silica, SAS, *Cab-O-Sil*

● **Chemical Name:** Silica

● **Empirical Formula:** SiO_2

● **Molecular Weight:** 60.08

● **Functional Category:**

Adsorbent, anticaking agent, emulsion stabilizer, glidant, suspending agent, tablet disintegrant, thermal stabilizer, viscosity-increasing agent.

● **Description:**

Colloidal silicon dioxide is a submicroscopic fumed silica with a particle size of about 15 nm. It is a light, loose, bluish-white-colored, odorless, tasteless, amorphous powder.

● **Typical properties:**

- Acidity/alkalinity: pH = 3.8–4.2 (4% w/v in aqueous dispersion)
- Density: 0.029-0.042 g/cm^3
- Melting point: 1600^0C
- **Solubility:**

  Practically insoluble in organic solvents, water, and acids, except hydrofluoric acid; soluble in hot solutions of alkali hydroxide. Forms a colloidal dispersion with water.

- **Pharmaceutical applications:**

  - Colloidal silicon dioxide is widely used in pharmaceuticals, cosmetics, and food products.
  - Colloidal silicon dioxide is also used to stabilize emulsions and as a thixotropic thickening and suspending agent in gels and semisolid preparations.
  - In aerosols, other than those for inhalation, colloidal silicon dioxide is used to promote particulate suspension, eliminate hard settling, and minimize the clogging of spray nozzles.
  - Colloidal silicon dioxide is also used as a tablet disintegrant and as an adsorbent dispersing agent for liquids in powders.

Table No: 12

Uses of Colloidal silicon dioxide with Concentration in Percentage(%)

USE	CONCENTRATION(%)
Aerosols	0.5-2.0
Emulsion stablisers	1.0-5.0
Glidant	0.1-1.0
Suspending and thickening agent	2.0-10.0

- **Stability and Storage:**

Colloidal silicon dioxide is hygroscopic but adsorbs large quantities of water without liquefying. Colloidal silicon dioxide powder should be stored in a well-closed container.

- **Incompatibilities:**

Incompatible with diethylstilbestrol preparations

MAGNESIUM STEARATE:[43]

● **Non-proprietary Names:**

BP: Magnesium Stearate
JP: Magnesium Stearate

● **Synonyms:**

Dibasic magnesium stearate, Magnesium distearate, Magnesium octadecanoate, Octadecanoic acid, Magnesium salt, Stearic acid, Magnesium salt.

● **Chemical Name:** Octadecanoic acid magnesium salt

● **Structural Formula:**

$[CH_3(CH_2)_{16}COO]_2Mg$

● **Empirical Formula:** $C_{36}H_{70}MgO_4$

● **Molecular Weight:** 591.24

● **Functional Category:** Tablet and capsule lubricant.

● **Description:**

- Magnesium stearate is a very fine, light white, precipitated or milled, impalpable powder of low bulk density, having a faint odor of stearic acid and a characteristic taste.
- The powder is greasy to the touch and readily adheres to the skin.

● **Typical properties:**

- Density**:** 1.092 g/cm^3
- Melting range: 117-150^{0}C
- Flowability: Poorly flowing, cohesive powder.
- **Solubility:**

  Practically insoluble in ethanol, ethanol (95%), ether and water. slightly soluble in warm benzene and warm ethanol (95%).

● **Pharmaceutical applications:**

Magnesium stearate is widely used in cosmetics, foods, and pharmaceutical formulations. Magnesium stearate is primarily used as lubricant in capsule and tablet manufacture at concentrations between 0.25% and 5.0% w/w. Magnesium stearate is hydrophobic and may retard the dissolution of a drug from a solid dosage form; the lowest possible concentration is therefore used in such formulations.

● **Incompatibilities:**

Incompatible with strong acids, alkalis, and iron salts. Avoid mixing with strong oxidizing materials.

ISOPROPYL ALCOHOL:[44]

● **Non-proprietary Names:**

BP: Isopropyl Alcohol

JP: Isopropanol

● **Synonyms:**

Dimethyl carbinol, IPA, isopropanol, 2-propanol, sec-propyl alcohol, rubbing alcohol.

● **Chemical Name:** Propan-2-ol

● **Empirical Formula:** C_3H_8O

● **Molecular Weight:** 60.1

● **Functional Category:** Disinfectant; solvent.

● **Description:**

Isopropyl alcohol is a clear, colorless, mobile, volatile, flammable liquid with a characteristic, spirituous odor resembling that of a mixture of ethanol and acetone; it has a slightly bitter taste.

- **Typical properties:**
  - Boiling point: 82.4^0C
  - Melting range: 88.58^0C
  - Flammability: Flammable.
  - **Solubility:**

    Miscible with benzene, chloroform, ethanol (95%), ether, glycerin, and water. Soluble in acetone; insoluble in salt

.● **Pharmaceutical applications:**

- Isopropyl alcohol is also used as a solvent both for tablet film-coating and for tablet granulation.
- Isopropyl alcohol (propan-2-ol) is used in cosmetics and pharmaceutical formulations, primarily as a solvent in topical formulations.
- Isopropyl alcohol has some antimicrobial activity and a 70% v/v aqueous solution is used as a topical disinfectant.

- **Safety:**
  - Isopropyl alcohol is widely used in cosmetics and topical pharmaceutical formulations. It is readily absorbed from the gastrointestinal tract and may be slowly absorbed through intact skin.
  - Prolonged direct exposure of isopropyl alcohol to the skin may result in cardiac and neurological deficits. In neonates, isopropyl alcohol has been reported to cause chemical burns following topical application.
  - Inhalation of isopropyl alcohol can cause irritation and coma.
- **Incompatibilities:**

Isopropyl alcohol may be salted out from aqueous mixtures by the addition of sodium chloride, sodium sulfate, and other salts, or by the addition of sodium hydroxide.

HYDROXYPROPYL METHYLCELLULOSE:[45]

● **Non-proprietary Names:**

BP: Hypromellose

JP: Hypromellose

● **Synonyms:**

Benecel MHPC, hydroxypropyl methylcellulose, HPMC, hypromellosum, Methocel, methylcellulose propylene glycol ether, methyl hydroxypropylcellulose, Pharmacoat.

● **Chemical Name:** Cellulose hydroxypropyl methyl ether.

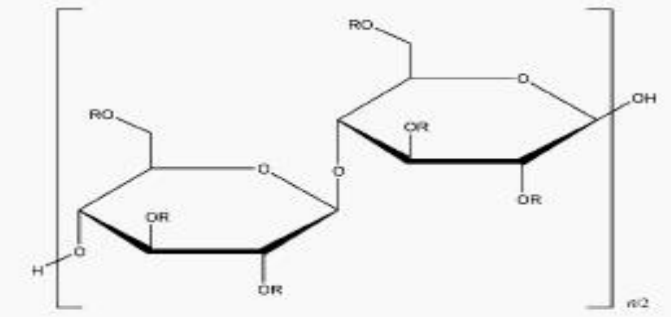
● **Empirical Formula and Molecular Weight:**

Molecular weight is approximately 10, 000–1,500, 00.

● **Functional Category:**

Coating agent, Controlled-release agent, Dispersing agent, Dissolution enhancer, Emulsifying agent, Forming agent, Foaming agent, Granulation aid.

● **Structural Formula:**



where R is H, CH_3, or $CH_3CH(OH)CH_2$

● **Description:**

Hypromellose is an odourless and tasteless, white or creamy-white fibrous or granular powder.

● **Typical properties:**

- Acidity/alkalinity: pH = 5.0–8.0 for a 2% w/w aqueous solution.
- Melting point: browns at 190-200^0 C; chars at 225-230^{0}C
- Glass transition temperature: 170-180^{0}C
- Loss on drying : ≤5.0%
- **Solubility:**

  Soluble in cold water; practically insoluble in hot water, chloroform, ethanol (95%), and ether; but soluble in mixtures of ethanol and dichloromethane and mixtures of methanol.

● **Pharmaceutical applications:**

Solid oral dosage forms	i) As tablet binder in either wet or dry granulations (2-5%w/w). ii) High viscosity grades as matrix formers for sustained drug release (10-80%w/w). iii) Depending on viscosity grade, concentrations of 2-20%w/w are used for film-forming solutions to coat tablets. iv) Lower viscosity grade – aqueous film coating. v) Higher viscosity grade – Nonaqueous coating.
Liquid oral dosage forms	As suspending or thickening agents at concentrations of 0.25 o 5.0%.
Ophthalmic preparations	Thickening agent to vehicles for eye drops and artificial tear solutions (0.45 to 1.0%).
Nasal preparations	At a concentration of 0.1%.
Topical preparations	As an emulsifier, suspending agent and stabilizing agent in topical gels and ointments.

● **Incompatibilities:**

Hypromellose is incompatible with some oxidizing agents. Since it is nonionic, hypromellose will not complex with metallic salts or ionic organics to form insoluble precipitates.

POLYMETHACRYLATES:[46,52]

- **Non-proprietary Names:**

BP: Methacrylic Acid–Ethyl Acrylate Copolymer (1 : 1), Methacrylic Acid–Ethyl Acrylate Copolymer (1 : 1) Dispersion 30 per cent, Methacrylic Acid–Methyl Methacrylate Copolymer (1 : 1), Methacrylic Acid–Methyl Methacrylate Copolymer (1 : 2) Polyacrylate Dispersion (30 per cent)

Ph.Eur: Methacrylic Acid - Methyl Methacrylate Copolymer (1:1), Methacrylic Acid - Methyl Methacrylate Copolymer (1:2)

- **Synonyms:**

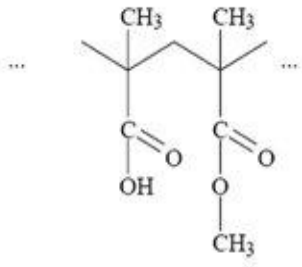
Acryl-EZE, Eastacryl, Eudragit, Kollicoat MAE, Polyacrylatis dispersion 30 per centum, Polymeric methacrylates.

- **Chemical Name:** Poly(methacylic acid-co-methyl methacrylate) 1:1

- **Molecular weight:** Approx. 125,000 g/mol

- **Functional Category:** Film-forming agent; tablet binder; tablet diluent.

- **Structural Formula:**



- **Description:**

EUDRAGIT® L 100 are anionic copolymers based on methacrylic acic and methyl methacrylate. It is a solid substance in form of a white powder with a faint characteristic odour. The ratio of free carboxyl groups to the ester is approximately 1 : 1.

● **Typical properties:**

- Acid value: 300-330
- True density: 0.831- 0.852 g/cm^3
- Glass transition Temperature (Tg): >130°C (+/- 5°C)
- **Solubility:**

  Powder form is soluble in alcohols and acetone and in 0.1N NaOH it gives clear solution, when it is cloudy. Practically insoluble in ethyl acetate, methylene chloride, petroleum ether and water.

● **Pharmaceutical applications:**

- Polymethacrylates are primarily used in oral capsule and tablet formulations as film-coating agents.
- Eudragit L-100 is used as an effective and stable enteric coating material for faster dissolution in the upper Bowel of intestine.

● **Stability and Storage:**

Dry powder polymer forms are stable at temperatures less than 30^0C. Above this temperature, powders tend to form clumps, although this does not affect the quality of the substance and the clumps can be readily broken up. Dry powders are stable for at least 3 years if stored in a tightly closed container at less than 30^0C.

TALC:[47]

● **Non-proprietary Names:**

BP: Purified Talc
JP: Talc

● **Synonyms:**

Hydrous magnesium calcium silicate, Hydrous magnesium silicate, Magnesium hydrogen metasilicate, Powdered talc, Purified french talc, Talcum.

● **Chemical Name:** Talc

● **Empirical Formula and Molecular Weight:**

Talc is a purified, hydrated, magnesium silicate, approximating to the formula $Mg_6(Si_2O_5)_4(OH)_4$. It may contain small, variable amounts of aluminum silicate and iron.

● **Functional Category:**

Anticaking agent, glidant, tablet and capsule diluent, tablet and capsule lubricant.

● **Description:**

- Talc is a very fine, white to greyish-white, odorless, impalpable, unctuous, crystalline powder. It adheres readily to the skin and is soft to the touch and free from grittiness.

● **Typical properties:**

- Acidity/alkalinity: pH = 7–10 (20% w/v aqueous dispersion)
- Moisture content: Talc absorbs insignificant amounts of water at 25^0C and relative humidities up to about 90%.
- **Solubility:**

  Practically insoluble in dilute alkalis and acids, organic solvents and water.

● **Pharmaceutical applications:**

- Talc was once widely used in oral solid dosage formulations as a lubricant and diluents.

Table No: 13

Uses of talc with concentration in percentage(%)

USE	CONCENTRATION(%)
Dusting powder	90.0-99.0
Glidant and tablet lubricant	1.0-10.0
Tablet and capsule diluent	5.0-30.0

● **Stability and Storage:**

Talc is a stable material and may be sterilized by heating at 160^0C for not less than 1 hour. Talc should be stored in a well-closed container in a cool, dry place.

TITANIUM DIOXIDE:[48]

● **Non-proprietary Names:**

BP: Titanium Dioxide
JP: Titanium Oxide

● **Synonyms:**

Brookite titanium dioxide, Hombitan FF-Pharma, Rutile titanium dioxide, Tioxide, titanic anhydride.

● **Chemical Name:** Dioxotitanium

● **Empirical Formula:** TiO_2

● **Molecular Weight:** 79.88

● **Functional Category:**

Coating agent, Opacifier and Pigment.

● **Description:**

White, amorphous, odorless, and tasteless, non hygroscopic powder.

● **Typical properties:**

- Moisture content: 0.44%
- **Solubility:**

  Practically insoluble in dilute sulfuric acid, hydrochloric acid, nitric acid, organic solvents, and water. Soluble in hydrofluoric acid and hot concentrated sulfuric acid. Solubility depends on previous heat treatment; prolonged heating produces a less-soluble material.

● **Pharmaceutical application:**

- Titanium dioxide is widely used in confectionery, cosmetics, and foods, in the plastics industry, and in topical and oral pharmaceutical formulations as a white pigment.
- It is used as a white pigment and opacifier.
- In pharmaceutical formulations, titanium dioxide is used as a white pigment in film-coating suspensions, sugar-coated tablets, and gelatin capsules.

● **Incompatibilities:**

Owing to a photocatalytic effect, titanium dioxide may interact with certain active substances, e.g. famotidine

PROPYLENE GLYCOL:[49]

● **Non-proprietary Names:**

BP: Propylene glycol

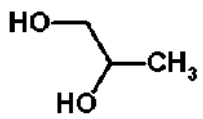
JP: Propylene glycol

● **Synonyms:**

1,2-Dihydroxypropane, 2-hydroxypropanol, Methyl ethylene glycol, Methyl glycol, Propane-1,2-diol, propylene glycolum.

● **Chemical Name:** 1,2-Propanediol

● **Structural Formula:**



● **Empirical Formula:** $C_3H_8O_2$

● **Molecular Weight:** 76.09

● **Functional Category:**

Antimicrobial preservative, solvent, stabilizer for vitamins, plasticizer**.**

● **Description:**

Propylene glycol is a clear, colorless, viscous, practically odorless liquid with a sweet , slightly acrid taste resembling that of glycerin.

● **Typical properties:**

- Boiling point: 188^0C
- Density: 1.038 g/cm^3
- Melting point: -59^0C
- **Solubility:**

  Miscible with acetone, chloroform, ethanol (95%),glycerin, and water. soluble at 1 in 6 parts of ether; not miscible with light mineral oil or fixed oils, but will dissolve some essential oils.

● **Pharmaceutical application:**

Propylene glycol has become widely used as a solvent. Propylene glycol is used as a plasticizer in aqueous film-coating formulations.

● **Storage:**

Propylene glycol is hygroscopic and should be stored in a well closed container, protected from light, in a cool, dry place.

● **Incompatibilities:**

Propylene glycol is incompatible with oxidizing reagents such as potassium permanganate.

TRIETHYL CITRATE:[50]

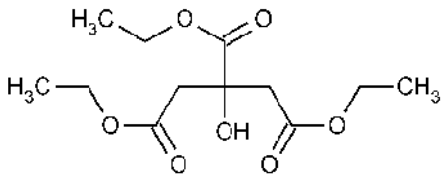
● **Non-proprietary Names:**

BP: Triethyl citrate
USP-NF: Triethyl citrate

● **Synonyms:**
Citric acid, Ethyl ester, Citroflex 2, Citrofol AI, TEC.

● **Chemical Name:** 2-Hydroxy-1,2,3-propanetricarboxylic acid triethyl ester

● **Structural Formula:**



● **Empirical Formula:** $C_{12}H_2O_7$

● **Molecular Weight:** 276.29

● **Functional Category:** Plasticizer, Solvent.

● **Description:**

Triethyl citrate is a clear, odorless, practically colorless, hygroscopic liquid.

● **Typical properties:**

- Acid value: 0.02
- **Solubility:**

  Soluble 1 in 125 of peanut oil, 1 in 15 of water. Miscible with ethanol (95%), and propan-2-ol.

● **Pharmaceutical application:**

- It is used to plasticize polymers in formulated pharmaceutical coatings. Triethyl citrate is also used as a direct food additive for flavoring, for solvency, and as an surface active agent.

● **Incompatibilities:**

Triethyl citrate is incompatible with strong alkalis and oxidizing materials.

QUINOLINE YELLOW LAKE:[30]

● **Synonyms:**

CI Food Yellow 13.

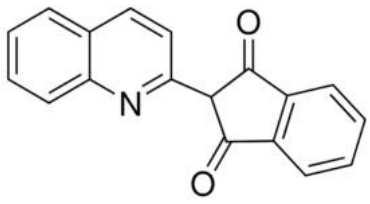
● **Chemical Name:**

Disodium 2-(1,3-dioxo-2-indanyl)-6,8-quinolinesulfates, Disodium 2-(2- quinolyl)-indan-1,3-dionedisulfonates

● **Empirical Formula:** $C_{18}H_9NNa_2O_8S_2$

● **Molecular Weight:** 477.38

● **Structural Formula:**



● **Description:**

It is yellow powder or granules in nature.

● **Typical properties:**

♦ **Solubility:**

It is soluble in water and sparingly soluble in ethanol

● **Pharmaceutical application:**

It is used as an coloring agent in pharmaceutical formulations.

● **Storage:**

It is stored in original container at ambient temperatures.

6.1. MATERIALS AND INSTRUMENTS

Table No: 14

List of Materials

S.No	Name of Ingredients	Category	Manufacturer's name
1.	Bisacodyl (BP)	Drug	J.P.N Pharma, India PVT Ltd
2.	Dibasic calcium phosphate	Filler	Rhodia
3.	Kaolin	Filler	Shijiazhuang
4.	Starch	Filler	Universal chem
5.	Lactose anhydrous	Filler	Loba chem
6.	Microcrystalline cellulose	Filler	FMC Biopolymer- USA
7.	Croscarmellose sodium	Disintegrant	FMC Biopolymer
8.	Sodium lauryl sulphate	Surfactant	Loba chem
9.	Povidone	Binder	Blagden speciality chemicals
10.	Aerosil	Glidant	Wacker chemical corporation
11.	Magnesium stearate	Lubricant	Kant health care
12.	Isopropyl alcohol	Vehicle	Ranchem
	COATING INGREDIENTS		
13.	HPMC 15 cps	Film polymer	Dow chemicals
14.	Eudragit- l- 100	Enteric coating ploymer	Evonik idustries
15.	Triethyl citrate	Plasticizer	Morflex
16.	Propylene glycol	Plasticizer	Fisher Scientific UK Ltd
17.	Purified talc	Anti- tacking agent	Vijaya minerals
18.	Quinoline yellow lake	Colorant	Vinayak corporation
19.	Titanium dioxide	Opaquant	Kronos ltd
20.	Purified water	Vehicle	Fourrts india, Chennai

Table No: 15

List of Equipments/Instruments

S.No.	Name of the Equipment	Manufacturer
1.	8 station compression machine	Accura, Ahmedabad
2.	Electromagnetic sieve shaker	EMS 8.
3.	Friability test apparatus (ET-2)	Electrolab, India.
4.	Bulk density apparatus	Campbell electronics, Thermonick.
5.	Automatic Coating Machine (Neocota 15 A)	Srimach, LTD
6.	Hardness tester	Monsanto.
7.	Disintegration test apparatus (ED-2L)	Electrolab, India.
8.	Dissolution apparatus (Disso 2000)	Lab India.
9.	pH meter (Digital 7007)	Lab india.
10.	IR Moisture balance	Citizen
11.	Electronic weighing balance (AR 2140)	Adventurer Mettler Toleda.
12.	Digital Vernier Caliper	Mitutoyo Corp., Japan.
13.	Hot air oven	Pathak electrical works.
14.	Stability chamber	Thermolab.
15.	HPLC with PDA/Binary system	Schimadzu Corp., Japan.

6.2. METHODOLOGY

PRE FORMULATION STUDIES:[15]

The basic concept of preformulation involves that almost all drugs are marketed as tablets, capsules or both. Prior to the development of these major dosage forms, it is essential that pertain fundamental physical and chemical properties of the drug molecule and other divided properties of the drug powder are determined. This information decides many of the subsequent events and approaches in formulation development. This first learning phase is known as preformulation.

Definition:

Preformulation is defined as the science of investigation of physio-chemical properties of a drug substance alone and when combined with excipients. Based on the physio-chemical properties, the drug delivery system can be designed. A thorough understanding of these properties may ultimately provide a rationale for the formulation design, or support the need for molecular modification.

Factors to be considered before starting preformulation studies:

a. The amount of drug available.
b. The physiochemical properties of the drug already known.
c. Therapeutic category and anticipated dose of compound.
d. The nature of information, a formulation should have or would like to have.

Classification of Preformulation Studies:[55]

Preformulation studies can be broadly classified into two classes:

- Fundamental properties.
- Derived properties.

The method and function characterization of fundamental and derived preformulation studies were given in the table below.

Table No: 16

Preformulation drug characterization in a structured program

Test	Method/ function Characterization
1. Fundamental	
1) UV spectroscopy	Simple assay
2) Solubility	Phase solubility/ purity
a) Aqueous	Intrinsic & pH effect
b) pKa	Solubility control , salt formation
c) Salt	Solubility, hygroscopicity & stability
d) Solvents	Vehicles & Extraction
e) ko/ w	Lipophillicity, structure activity
f) Dissolution	Biopharmacy
3) Melting point	DSC-polymorphism hydrate & solvent
4) Assay development	UV, HPLC, TLC
5) Stability	
In Solution	Thermal, hydrolysis, pH
In solid state	Oxidation, proteolysis metal ion
2. Derived	
6) Microscopy	Particle size and morphology
7) Bulk density	Tablet and capsule formation
8) Flow properties	Tablet and capsule formation
9) Compression properties	Acid / excipient choice
10) Excipient compatibility	Preliminary screen by DSC, Conformation by TLC

Scope:

Use of preformulation parameters maximizes the chances in formulating an acceptable, safe, efficacy and stable product and at the same time provides the basis for optimization of drug product quality.

The present work has been initiated with the prefomulation studies for the following parameters. The evaluation parameters was done according to British pharmacopoeia.

Evaluation of Active pharmaceutical ingredient (API):

A. Physio - Chemical evaluation:

1. Description
2. Solubility analysis
3. Moisture content
4. Bulk density
5. Tapped density
6. Particle size determination

B. Drug- Excipient compatibility studies:

1. Physical appearance
2. FT-IR studies

A. Physio - chemical evaluation:

1. Description:

A typical preformulation should begin with the description of the drug substance, that is colour, odour and taste of the new drug and the results are tabulated in ***Table No:30.*** Some of the terminologies suggested to describe the new drug substances are given below.

Table No: 17

Terminologies indicating the product characters

Colour	Odour	Taste
Off- white	Pungent	Acidic
Cream	Fruity	Bitter
yellow	Aromatic	Bland
Tan	Sulfurous	Sweet
Shiny	Odourless	Tasteless

2. Solubility analysis:[55]

Basically solubility is an important parameter for physio-chemical properties for determining the systemic absorption and its therapeutic efficacy. The solubility of drug was determined by dissolving the drug in the various solvent system like water, acetone,

isopropyl alcohol and ethanol in 250ml beaker. The results were shown in ***Table No: 31***. The approximate solubilities of pharmacopoeial and national formulary substances are indicated by the descriptive terms in accompanying given below.

Table No: 18

SOLUBILITY SPECIFICATIONS

Descriptive terms	**Approximate volume of solvent in milliliters per gram of solute**
Very soluble	Less than 1
Freely soluble	From 1 to 10
Soluble	From 10 to 30
Sparingly soluble	From 30 to 100
Slightly soluble	From 100 to 1000
Very slightly soluble	From 1000 to 10,000

3.Moisture content:

The moisture means 'wetness', which influences the chemical stability, dissolution rate and polymer film permeation on storage under stability condition. The moisture content was determined by the IR moisture balance by adding the known quantity of drug say 1 gm was weighed on the sample pan. The sample was dried until anhydrous at 60°c by the use of IR radiation. The percentage of moisture content of the drug can be determined as the end point display when all the moisture in the sample has been removed by the radiation. The results were shown in ***Table No: 32.***

4. Bulk density:[21]

The bulk density is the ratio between an given mass of a powder and its bulk volume. It is expressed as g/ml. Weighed quantity of bisacodyl powder were transferred into a 50 ml measuring cylinder without tapping during transfer the volume occupied by the powder was measured. It is given by the formula. The results were shown in ***Table No: 33.***

$$\text{Bulk density}(D_b) = \frac{m}{V_o}$$

where,

m = Mass of powder.

V_o = Bulk volume of the powder.

5. Tapped density:[21]

Tapped density is achieved by tapping the measuring cylinder which contains the sample for certain tapping's mechanically. During tapping, particles gradually pack more efficiently, the powder volume decreases and the tapped density increases. After observing the initial volume of powder occupied in the 100ml measuring cylinder and then subjected to 50 tap's in the bulk density apparatus (Campbell, thermonik). After 50 tappings the final volume is noted down and the results are tabulated. It is calculated by the formula. The results were shown in ***Table No: 33.***

$$\text{Tapped density } (D_t) = \frac{m}{V_t}$$

where,

m = Mass of powder

V_t = Volume of the powder occupied after tapping

6. Particle Size Determination:[3]

In case of tablets, size influences the flow and the mixing efficiency of powders and granules. Size of the particle also an important factor in stability. Fine materials are relatively more open to attack from atmospheric oxygen, the humidity and interacting excipients than

are coarse materials. The particle size determination is done by various methods like sieve method, microscopic method, sedimentation technique, coulter counter technique and low angle light scattering technique.

Particle size distribution of the drug was estimated by sieving method. The sieves are stacked on top of one another in ascending order. The test powder, for example 10gm, was placed on the top sieve. The sieves are tightly screwed and subjected to agitation for 5 minutes. After agitation the weight of powder retained on each sieve was accurately weighed. Percentage of powder retained on each sieve was calculated by using the following formula. The results were tabulated in the ***Table No: 34.***

Percentage retained =

$$\frac{\text{Powder retained on each sieve}}{\text{Initial weight}} \times 100$$

B. DRUG- EXCIPIENT COMPATIBILITY STUDIES:

Incompatibility between drug and excipient can alter stability and bioavailability of drugs, thereby, affecting its safety and/or efficacy. Study of drug–excipient compatibility is an important process in the development of a stable solid dosage form. Drug–excipient compatibility testing at an early stage helps in the selection of excipient that increases the probability of developing a stable dosage form. In the tablet dosage forms, the drug is in intimate contact with one or more excipients, the latter could affect the stability of the drug. The drug excipient compatibility studies was determined from the physical compatibility studies and FT-IR studies.

I. Physical compatibility studies:

API was mixed well with all excipients in binary ratio in an mortar and small portion of this mixed powder was placed in a cleaned and dried vial. This vial was kept in stability chamber at $40^0C \pm 2^0C$/ 75±5% RH for 2 weeks. Physical observation has been carried out visually at the initial stage and after 2 weeks exposure to the stated conditions. The results were tabulated in ***Table No:35.***

II. FT-IR compatibility studies:[10,12,24,57]

Physical compatibility studies were assured by FT-IR studies. In this, crude drug sample, drug-polymer mixtures and the final formulation were chosen for the study. Potassium Bromide pellet method was used in this study. Initially, potassium bromide was powdered and dried in oven. Dried potassium bromide powder was mixed with little quantity of each test sample, thoroughly triturated in mortar and pestle. A portion of mixture was compressed using IR pelletizing press. Then the KBr pellet was placed in sample holder of FT-IR spectrophotometer. The spectra were recorded in the wave number region of 4000-400cm^{-1}. In each case, the spectra was compared with the pure bisacodyl spectrum to detect the interactions between drug and excipients. The analysed FT-IR spectra and interpretation data for the drug sample and the drug- excipient mixtures were shown in the ***Figure No:7,8,9,10,11,12,13,14 and Table No: 36, 37, 38,39, 40, 41, 42 and 43 .***

Table No: 19

Protocol for Drug-Excipient compatibility studies

S.NO	DRUG AND EXCIPIENTS	RATIO
1.	Drug	1
2.	Drug + DCP	1:1
3.	Drug + Kaolin	1:1
4.	Drug + Lactose	1:1
5.	Drug + Starch	1:1
6.	Drug + CCS	1:1
7.	Drug+ PVP	1:1
8.	Drug + SLS	1:1

Formulation of bisacodyl enteric- coated tablet:

- **Selection of process:**

Micrometric studies has been carried out for the active ingredient, bisacodyl. Based on the results observed it was concluded that the drug is not suitable for direct compression method due to fine particle size and poor flow characteristics. So, the enteric coated tablet of bisacodyl was prepared by wet granulation technique. All the tablet ingredients was accurately weighed as mentioned in ***Table No:20.*** The average weight of each core tablet was fixed initially 120 mg and that was changed to 100mg on further trials.

Table No: 20

FORMULATION TRIAL BATCHES

S.NO	INGREDIENTS (mg)	FORMULATION CODE						
		F1	F2	F3	F4	F5	F6	F7
1.	Bisacodyl	5.1	5.1	5.1	5.1	5.1	5.1	5.1
2.	Dibasic calcium phosphate	0	10	15	19	19	19	19
3.	Kaolin	13	18	15	25	18	18	4
4.	Starch	32	30	26	0	20	20	24
5.	Lactose anhydrous	40	40	27	20	0	27	37
6.	Microcrystalline cellulose	0	0	0	20	27	0	0
7.	Croscarmellose sodium	3	3	2	2	2	2	2
8.	Lactose anhydrous	13	0	0	0	0	0	0
9.	Sodium lauryl sulphate	0	0	1	0	0	0.3	0.5
10.	Povidone K-30	3	3	3	4	4	4	3
11.	Isopropyl alcohol	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
12.	Starch	5	6	4	2	2	2	2
13.	Croscarmellose sodium	6	5	2	3	3	3	3
14.	Colloidal silicon dioxide	0.2	0.2	0.25	0.25	0.25	0.25	0.25
15.	Magnesium stearate	0.2	0.2	0.25	0.25	0.25	0.25	0.25
	Average weight	120mg	120mg	100mg	100mg	100mg	100mg	100mg

Table No: 21

PERCENTAGE OF INGREDIENTS USED IN TRIAL BATCHES

S.NO	INGREDIENTS (%)	FORMULATION CODE						
		F1	F2	F3	F4	F5	F6	F7
1.	Bisacodyl	4.25	4.25	5.1	5.1	5.1	5.1	5.1
2.	Dibasic calcium phosphate	0	8.33	15	19	19	19	19
3.	Kaolin	10.83	15.0	15	25	18	18	4
4.	Starch	26.6	25.0	26	0	20	20	24
5.	Lactose anhydrous	33.3	33.3	27	20	0	27	37
6.	Microcrystalline cellulose	0	0	0	20	27	0	0
7.	Croscarmellose sodium	2.5	2.5	2	2	2	2	2
8.	Lactose anhydrous	10.83	0	0	0	0	0	0
9.	Sodium lauryl sulphate	0	0	1	0	0	0.3	0.5
10.	Povidone K-30	2.5	2.5	3	4	4	4	3
11.	Isopropyl alcohol	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
12.	Starch	4.16	5	4	2	2	2	2
13.	Croscarmellose sodium	5	4.16	2	3	3	3	3
14.	Colloidal silicon dioxide	0.16	0.16	0.25	0.25	0.25	0.25	0.25
15.	Magnesium stearate	0.16	0.16	0.25	0.25	0.25	0.25	0.25
	Average weight	120mg	120mg	100mg	100mg	100mg	100mg	100mg

Manufacturing procedure:

Note: During all stages of the manufacturing process the temperature and humidity shall be maintained at **$25^0 \pm 5^0$C and 30 ±5% RH**

Step 1: Weighing: Accurately weighed specified quantity of ingredients: Bisacodyl, Kaolin, Dibasic calcium phosphate, Starch, Croscarmellose sodium and Lactose anhydrous.

Step 2: Co-Sifting: The above materials were co-sifted together by geometric dilution method through #30 mesh and #60 meshes and placed in a separate polythene bag and they are used as dry mix. [***Note:*** Dry mix of formulations F1 to F4 were sifted by physical mixing where as formulations F5 to F7 were milled and sifted through appropriate meshes.]

Step 3: Preparation of Binder solution :

Accurately weighed povidone is added to isopropyl alcohol and stirred well to get a clear solution and this clear solution used as binder solution.

Step 4: Granulation: The sifted materials were mixed for 5 mins in a polythene bag before granulating and transferred to a vessel and granulated with required quantity of binder solution by kneading method (hand granulation).

Step 5: Drying: The granules were dried in hot air oven at 40-50^{0}C . then semi dried granules were passed through sieve No. 20, and continued the drying till the moisture content of granules is less than 1.0 %. Then after obtaining the optimum moisture content, granules were removed from the oven.

Step 6: Sizing of granules : The dried granules were sifted through #30 mesh to get uniform particle size.

Step 7: Mixing & Lubrication: The above granules were mixed with croscarmellose sodium. and mixed well. Finally lubricated with the required quantity of colloidal silicon dioxide and magnesium stearate after sifting it through #60mesh for 2 mins.

Step 8: Compression: The lubricated granules was then compressed into tablets with an average weight 120 mg initially using 8.00 mm punches.

Step 9: Seal coating

Step10: Enteric coating

Figure No: 5

Formulation Flow chart of Wet Granulation Method for Trials F1 To F4

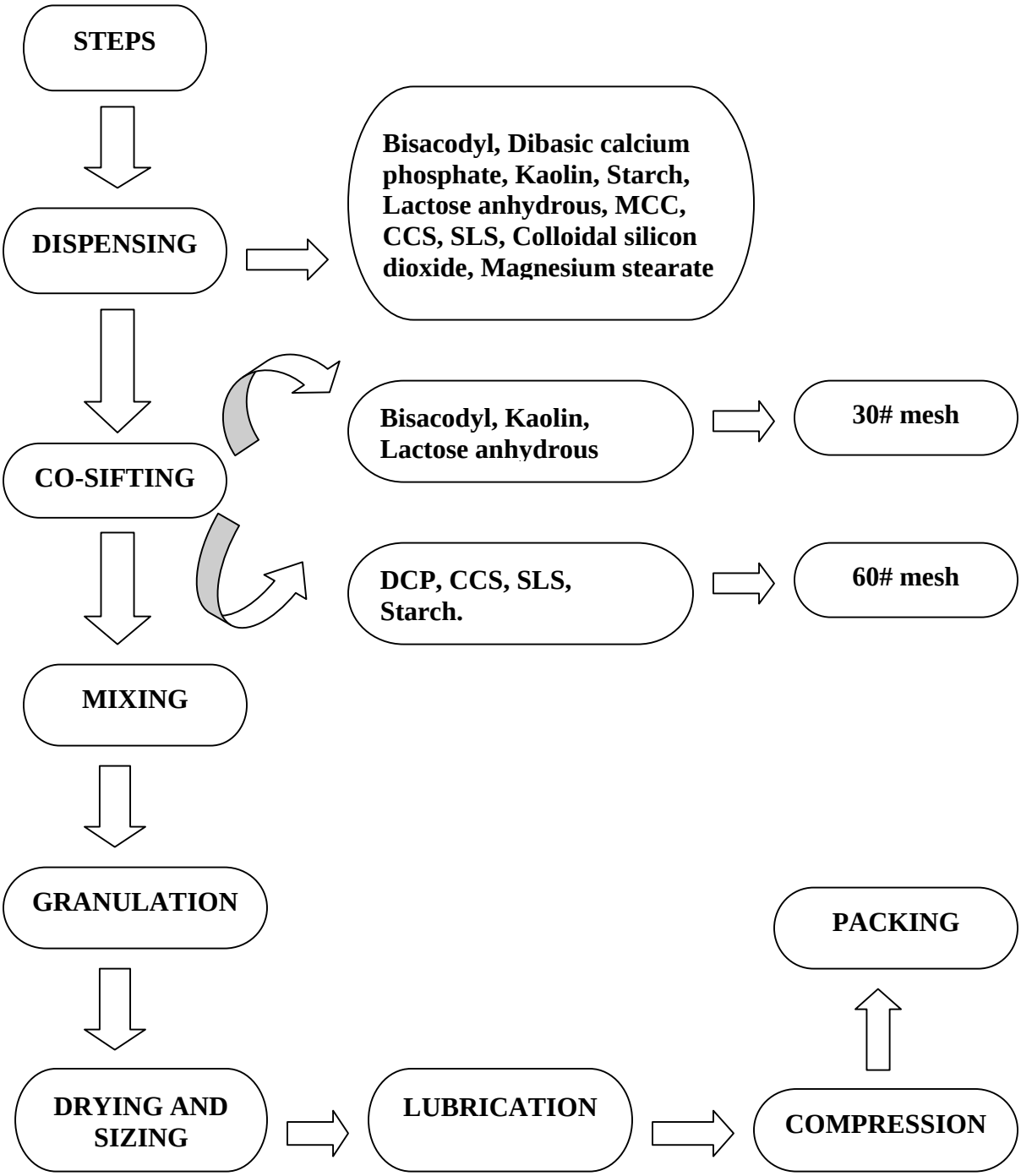
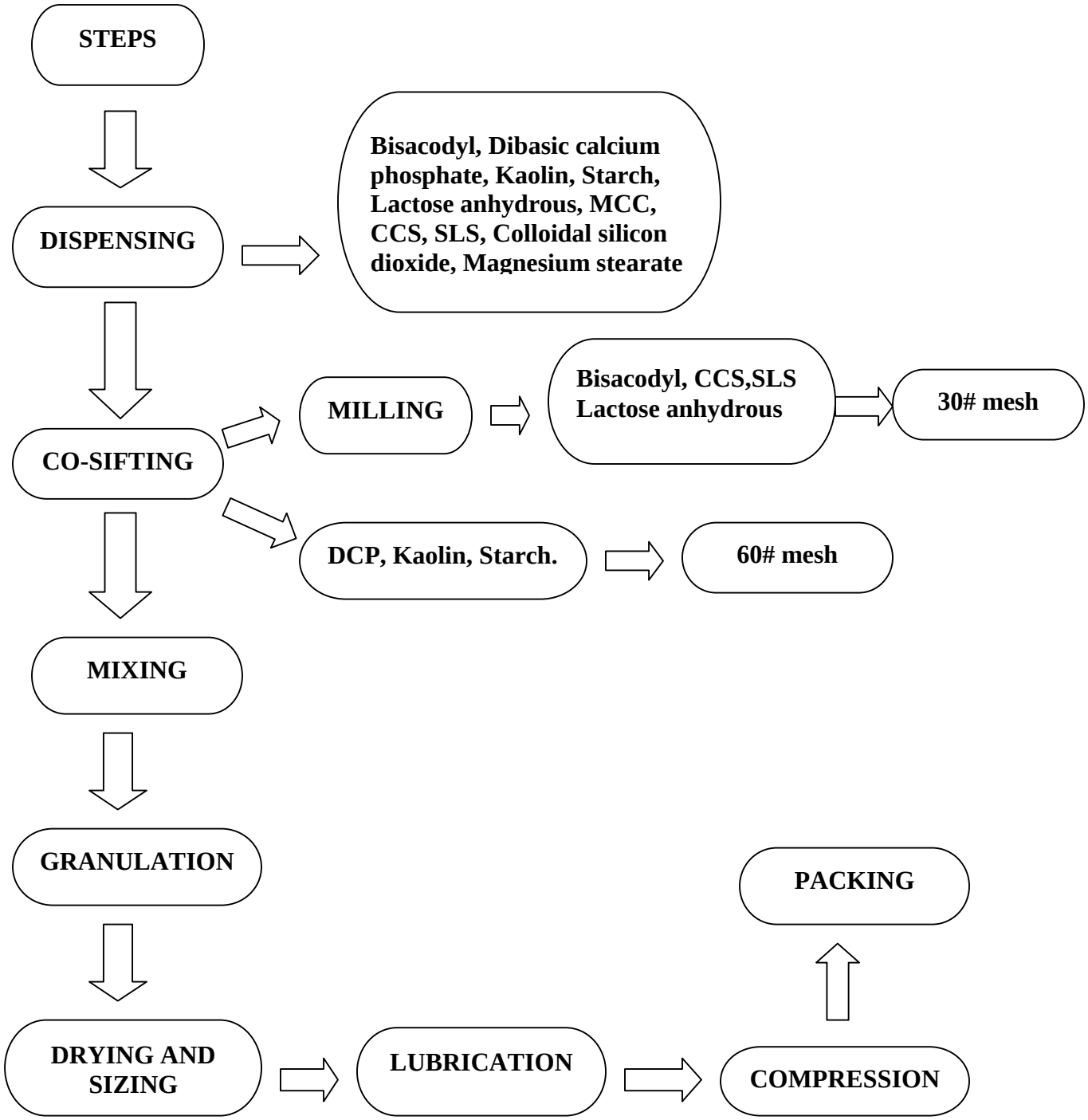


Figure No: 6

Formulation Flow chart Of Wet Granulation Method For Trials F5 To F7



COATING FORMULA:

Seal coating:

Seal coating is important for preventing direct interaction between bisacodyl and polymer. Seal coating is performed for the core tablet of formulation (F7). When 2% build up is given, the weight of the seal coated tablet was found to be 102mg per tablet.

Table No: 22

Composition of Ingredients for Seal Coating

S.No	Ingredients	Quantity(gm)
1	HPMC 15 cps	2.4
2	Talc	0.6
3	Titanium dioxide	0.6
4	Propylene glycol	0.4
5.	Purified water	Q.S

Preparation of seal coating solution:

Weighed accurately a required quantity of HPMC 15 cps and soaked in water for 30 mins, and stirred until it swells. Mean while talc and titanium dioxide was triturated in a mortar and added to the above solution and stirred. followed by propylene glycol as plasticizer is added furtherly and stirred**.** Filter the above solution in #100 mesh. Finally the volume were made up to the required quantity with purified water**.**

Enteric Coating:

Enteric coating is performed to protect the drug from acidic environment. The seal coated tablets were subjected to enteric coating where the weight of the enteric coated tablets was found to be 109.14mg when 7% build up is given.

Table No: 23

Composition of Ingredients for Enteric Coating

S.No	Ingredients	Quantity (gm)
1	Poly methacryllic acid -methyl acrylate(1;1)	7.854
2	Talc	2.142
3	Titanium dioxide	1.856
4	Triethyl citrate	1.856
6	Quinoline yellow lake	0.572
7	Purified water	Q.S

Preparation of Enteric Coating solution:

A required quantity of Methacrylic acid copolymer powder, was weighed accurately and kept stirring with the required quantity of water. Mean while, talc, titanium dioxide and quinoline yellow lake were triturated separately in a mortar until making a paste by adding the water and added to the above solution and stirred. Filter the above solution with #100 mesh. Finally the volume were maked up to the required quantity with purified water**.**

COATING PARAMETERS:

Table No: 24

Operation condition for Seal and Enteric Coating Process

Specifications	Range	
	Seal coating	**Enteric coating**
Pan diameter	12”	12”
Speed of pan revolution	8-10 rpm	10-12 rpm
Distance of spray gun	5-6”	5-6”
Spray nozzle diameter	1.2 mm	1.2 mm
Spray rate	2.5-3 ml /min	1.5 -2.0 ml /min
Dry air temperature	50 ± 5/ 30 mins	50 ± 5^0C / 30 mins
Coating time	2 hours	4 hours
Bed temperature	30-40^{0}C	30-40^{0}C

Evaluation of pre compression parameter for powder blend:

The pre compression parameters for the powder blend or granules were evaluated for the following parameters. The results were tabulated in ***Table No: 43 and 44.***

1. Bulk density
2. Tapped density
3. Compressibility index (%)
4. Hausner’s ratio
5. Moisture content
6. Particle size determination

1. Bulk density:[21]

The bulk density is the ratio between an given mass of powder and its bulk volume. It is expressed as g/ml. Weighed quantity of granules were transferred into a 50 ml measuring cylinder without tapping during transfer the volume occupied by the powder was measured. It is given by the formula.

$$\textbf{Bulk density } (D_b) = \frac{m}{V_o}$$

where,

m = Mass of powder.

V_o = Bulk volume of the powder.

2. Tapped density:[21]

Tapped density is achieved by tapping the measuring cylinder which contains the sample for certain tapping's mechanically. During tapping, particles gradually pack more efficiently, the powder volume decreases and the tapped density increases. After observing the initial volume of powder occupied in the 100ml measuring cylinder and then subjected to 50 tap's in the bulk density apparatus (Campbell, thermonik). After 50 tappings the final volume is noted down and the results are tabulated. It is calculated by the formula.

$$\textbf{Tapped density } (D_t) = \frac{m}{V_t}$$

where,

m = Mass of powder.

V_t = Volume of the powder occupied after tapping.

3. Compressibility index:[28]

. Compressibility is the ability of powder to decrease in volume under pressure using bulk density and tapped density the percentage compressibility of powder were determined, which is given as carr's compressibility index. It is indirectly related to the relative flow rate. Carr's compressibility index was determined by the given formula.

Compressibility index =

$$\frac{V_0 - V_f}{V_0} \times 100$$

where,

V_0 = Unsettled apparent volume.

V_f = Final tapped volume.

Table No: 25

Carr's Index

Compressibility index (%)	Flow description
5-15	Excellent
12-16	Good
18-21	Fair
23-28	Passable
28-35	Poor
35-38	Very poor
>40	Very, very poor

4. Hausner's ratio:[28]

It is very important parameter to be measured since it affects the mass of uniformity of the dose. It is usually predicted from hausner's ratio and angle of repose Measurement Hausner's ratio related to interparticle friction and, as such could be used to predict powder flow properties. **Table No: 26** shows the flow description and corresponding hausner's ratio. It is determined by the formula.

$$\text{Hausner Ratio} = \frac{V_0}{V_f}$$

where,

V_0 = Unsettled apparent volume.

V_f = Final tapped volume.

Table No: 26

Hausner's ratio

Type of Flow	Hausner's ratio
Excellent	1.0– 1.11
Good	1.12 – 1.18
Fair	1.19 – 1.25
Passable	1.26 – 1.34
Poor	1.35 – 1.45
Very poor	1.46 – 1.59
Very, Very poor	>1.60

5. Moisture content:[28]

The moisture means 'wetness', which influences the chemical stability, dissolution rate and polymer film permeation on storage under stability condition. The moisture content was determined by the IR moisture balance by adding the known quantity of drug say 1 gm was weighed on the sample pan. The sample was dried until anhydrous at 60˚c by the use of IR radiation. The percentage of moisture content of the drug can be determined as the end point display when all the moisture in the sample has been removed by the radiation.

6.Sieve analysis:[3]

The purpose of particle size analysis in pharmacy is to obtain quantitative data on the size, distribution, and shapes of the drug and other components to be used in pharmaceutical formulations. The particle size determination is done by various methods like sieve method, microscopic method, sedimentation technique, coulter counter technique and low angle light scattering technique.

Particle size determination of the drug was estimated by sieving method. The sieves are stacked on top of one another in ascending order. The test powder, for example 10gm, was placed on the top sieve. The sieves are tightly screwed and subjected to agitation for 5

minutes. After agitation the weight of powder retained on each sieve was accurately weighed. Percentage of powder retained on each sieve was calculated by using the following formula.

Percentage retained =

$$\frac{\text{Powder retained on each sieve}}{\text{Initial weight}} \text{ X 100}$$

Evaluation of Post Compression parameters for compressed tablets:

The compressed tablets were evaluated for the following parameters and The results were tabulated in the ***Table No: 46 and 47.***

1.General appearance
2. Hardness test
3. Thickness
4. Friability
5. Weight variation test
6. Disintegration test
7. *Invitro* dissolution study

1. General appearance:[51]

The compressed tablets should be free from cracks, depression, pinholes etc. The colour and polish of the tablets should be uniform on whole surface. The surface of the tablets should be smooth. It is done by visual observation.

2. Hardness test:[22]

Tablets require certain amount of strength or hardness to withstand mechanical shocks of handling in manufacture, packaging and shipping. Hardness can be defined as the strength of the tablet to withstand the pressure applied. In this test, a tablet was laced between two anvils, force was applied to the anvils and the crushing strength that just causes the tablet to break is recorded. Hence hardness is sometimes referred to as "Crushing Strength".

It was measured using Monsanto tablet hardness tester. The values were expressed in kg/cm^3.

3.Thickness:[23]

Tablet thickness is an important parameter to be controlled to facilitate packaging. Tablet thickness, at constant compressive load, varies with changes in die fill, with particle size distribution and packing of the particle mix being compressed. Tablet thickness must be controlled within a ±5% variation of a standard value. The thickness of the tablets was measured by using digital vernier calipers. The thickness was denoted in millimeter.

4. Friability:[29]

Friability is a measure of the resistance of the tablet to abrasion. The friability of tablets was determined by using Roche friabilator. Tablets were weighed equivalent to 6.5g and placed in friabilator and rotated at 100 revolution's for 5 minutes. Then the tablets were taken out, dedusted and reweighed. The percentage friability of the tablets were calculated by the formula.

$$\% \text{ Friability (F)} = \frac{W_O - W_f}{W_f} \times 100$$

Where,

W_O = Initial weight of tablets

W_f = Final weight of tablets

5. Weight variation test:[5]

Weight variation test is performed to check that the manufactured tablets have an uniform weight. Randomly weighed 20 tablets and calculated the average weight. Not more than two of the individual weights deviate from the average weight by more than the percentage deviation shown in table and more deviated by more than twice that percentage. The percentage deviation of the tablets were calculated by the formula.

Percentage deviation =

$$\frac{\text{Individual weight of tablet - Average weight of tablet}}{\text{Average weight of tablet}} \times 100$$

Table No: 27

Weight variation table with percentage deviation

S.No	Average weight (mg)	Maximum percentage deviation allowed (%)
1	130mg or less	±10
2	130mg to 324mg	±7.5
3	More than 324mg	±5

6. Disintegration test:[11]

Disintegration is the first physical change observed for a drug when it enters into the body, thus to see simulate the disintegration of the tablet in the body the disintegration test is performed. The disintegration test for bisacodyl enteric coated tablets was carried out using USP tablet disintegration tester about the temperature at $37^{o}C \pm 2^{\circ}C$ for 2 hours in 500ml 0.1N HCL (pH 1.2), then the medium was changed to pH 7.4 phosphate buffer and tested for 45 mins.

Table No: 28

Acceptance criteria for Enteric coated tablets

Type of tablet	Medium	Disintegration Time
Enteric- Coated tablets	**0.1N Hydrochloric acid (pH 1.2)**	Should not disintegrate in 120 mins
	Mixed phosphate buffer(pH 7.4)	45mins

7. *In vitro* dissolution studies:[53]

Dissolution at Acid stage medium:

- **Apparatus:** Type II paddle
- **Speed:** 100 rpm
- **Duration:** 2 hours
- **Time points:** Up to 2 hours
- **Temperature:** 37˚C ± 0.5˚C
- **Medium:** 500ml of 0.1N HCL
- **Sample withdrawn:** 10ml

Dissolution media Preparation:

Preparation of 0.1N HCL: 8.5 ml of concentrated HCL was added to 1000 ml of purified water and the pH was adjusted to 1.2.

Standard Preparation : Accurately weighed and transferred 10.0 mg of bisacodyl in 100 ml standard flask, add 5 to 10 ml 0.1N HCL to dissolve the drug completely and volume was make up with same medium up to 100ml. From this primary stock solution pipette out 10 ml and transferred to 100 ml standard flask and made up the volume with 0.1N HCL (pH 1.2) medium.

Dissolution procedure: Apparatus was set as per above conditions, one tablet was placed in each of the six dissolution bowls containing 500ml of 0.1N HCL as medium and the dissolution test was performed for 2 hours. An Aliquots of the dissolution medium was withdrawn at the specified time and filtered.

Sample injection procedure:

50 µl of sample preparation and standard preparation were injected into the liquid chromatograph and recorded the chromatogram. The major peaks were recorded and calculated for the assay quantity of bisacodyl in percentage from the peak areas of standard and sample preparation and the percentage of bisacodyl drug released at the end of 2 hours was calculated by the mentioned formula.

BP limits : NMT 5% of the stated amount of bisacodyl is dissolved in 2 hrs.

Dissolution at Buffer stage medium:

- **Apparatus:** Type II paddle
- **Speed:** 100 rpm
- **Duration:** 45minutes
- **Time points:** 15, 30, 45 minutes
- **Temperature:** $37^0C \pm 0.5^0C$
- **Medium:** 900ml of phosphate buffer pH 7.4
- **Sample withdrawn:** 10ml

Dissolution media Preparation:

Preparation of phosphate buffer (pH 7.4): 7.80g of sodium dihydrogen orthrophosphate in sufficient water to produce 1000ml. Add 5.0g of sodium dodecyl sulfate, heat to dissolve and adjust the pH to 7.4.

Standard Preparation :

Accurately weighed and transferred 56.0 mg of bisacodyl in 100 ml standard flask, add 5 to 10 ml acetonitrile to dissolve the drug completely and volume was make up with the same medium upto 100ml. From this primary stock solution pipetted out 10 ml and transferred to 100 ml standard flask and made up the volume with pH 7.4 buffer medium.

Dissolution procedure:

Apparatus was set as per above conditions, one tablet was placed in each of the six dissolution bowls containing 900ml of pH 7.4 as buffer medium and the dissolution test was performed for 45 minutes. An Aliquots (10ml) of the dissolution medium was withdrawn at the specified time points from each bowl and filtered through 5 µm filter paper.

Sample injection Procedure:

50 µl of sample preparation and standard preparation were injected into the liquid chromatograph and recorded the chromatogram. The major peaks were recorded and calculated for the assay quantity of bisacodyl in percentage from the peak areas of standard

and sample preparation and the percentage of bisacodyl drug released at the end of 45minutes was calculated by the mentioned formula

% Release =

$$\frac{AT}{AS} \times \frac{WS}{100} \times \frac{1}{100} \times \frac{900}{5} \times \frac{98.15}{100} \times 100$$

where,

AT= Sample area

AS = Standard area

WS = Working standard

BP limits : NLT 75% of the stated amount of bisacodyl is dissolved in 45mins.

ASSAY BY HPLC METHOD:[53]

Chromatographic conditions:

The chromatographic conditions were set as per BP specifications.

Apparatus:	HPLC
Column:	A stainless steel column (25cm x 4.6mm) packed with base- deactivated octadecylsilyl silica gel (5µm) usually water's symmetry (C_{18}) is suitable.
Wavelength:	265nm
Flow rate:	1.5ml/min
Column temperature:	Ambient
Detector:	Photodiode array
Inject volume:	50µL

Preparation of mobile phase:

A mixture of 45 volumes of acetonitrile and 55 volumes of 0.025M ammonium formate previously adjusted to pH 5.0 with anhydrous formic acid.

Preparation of diluent:

A mixture of 4 volumes of glacial acetic acid, 30 volumes of acetonitrile and 66 volumes of distilled water was prepared as diluent for assay.

Preparation of phosphate buffer (pH 7.4):

7.80g of sodium dihydrogen orthrophosphate in sufficient water to produce 1000ml. Add 5.0g of sodium dodecyl sulfate, heat to dissolve and adjust the pH to 7.4.

Preparation of standard solution:

50mg of bisacodyl RS was accurately weighed and transferred into a 100ml clean dry volumetric flask and dissolve in little quantity of acetonitrile, sonicate for 5 minutes and make up the volume. From this stock solution 5 ml was transferred into a 50 ml volumetric flask and make up the volume with buffer medium.

Preparation of sample solution:

For the estimation in dosage form, 20 tablets were weighed and powdered. Amount equivalent to 10 mg of bisacodyl from powdered tablets was accurately weighed and transferred to 200 ml volumetric flask, added about 10 ml of acetonitrile mixture and sonicate for 15 minutes. Cool the solution to room temperature and make up the volume with same diluent. Filter a portion of above solution and pipette out 5 ml of the filtrate and transferred to 50 ml volumetric flask and make up the volume with buffer.

Sample injection procedure:

20 µl of filtered portion of the standard preparation (five injections) and sample preparation were separately injected into the chromatographic system. The chromatograms was recorded and the responses were measured for the major peaks. The content of bisacodyl present in each tablet was calculated using the following expression.

% Content =

$$\frac{AT}{AS} \times \frac{WS}{100} \times \frac{5}{50} \times \frac{50}{Spl\ Wt} \times \frac{P}{100} \times Avg.Wt \times 100$$

where,

AS = Standard area

AT = Sample area

WS = Standard weight

Spl Wt = Sample weight

Avg.Wt = Sample average weight

Comparative *Invitro* dissolution profile study:[9]

In recent years, FDA has placed more emphasis on a dissolution profile comparison in the area of post-approval changes and biowaivers. Under appropriate test conditions, a dissolution profile can characterize the product more precisely than a single point dissolution test. A dissolution profile comparison between pre-change and post-change products for SUPAC related changes, or with different strengths, helps assure similarity in product performance and signals bio in equivalence. Comparison of therapeutic performances of two medicinal products containing the same active substance is a critical means of assessing the possibility of alternative using between the innovator and any essentially similar medicinal product. Dissolution profiles of two products can be considered similar by virtue of

- Overall profile similarity, and
- Similarity at every dissolution sample time point.

A simple model independent approach uses a difference factor (f_1) and a similarity factor (f_2) to compare the dissolution profiles. The difference factor calculates the percentage difference between the two curves at each time point and is measurement of the relative error between the two curves:

$$f_1 = \{[\sum_{t=1}^{n} | R_t - T_t |]/[\sum_{t=1}^{n} R_t]\} \bullet 100$$

where, n is the number of time points, R_t is the dissolution value of the reference batch at time t and T_t is the dissolution value of the test batch at time t.

The similarity factor f_2 is a logarithmic reciprocal square root transformation of the sum of squared error and is a measurement of the similarity in the percent dissolution between the two curves.

$$f_2 = 50 \bullet \log \{[1+(1/n)\sum_{t=1}^{n} (R_t - T_t)^2]^{-0.5} \bullet 100\}$$

General procedure*:*

i. Determine the dissolution profile of two products (6 units each) of the test and reference products.

ii. Using the mean dissolution values from both the curves at each time interval, calculate the difference factor (f_1) and similarity factor (f_2) using the above equations.

iii. For curves to be considered similar, f_1 values should be close to 0, and f_2 values should be close to 100. Generally, f_1 values upto 15 (0-15) and f_2 values greater than 50 (50-100) ensures sameness or equivalence of the two curves.

The comparative dissolution study was performed to determine the similarity of dissolution profiles for bisacodyl enteric coated tablets between the innovator product (DULCOLAX) with the optimized formulation. **(F7)** The results were tabulated in ***Table No: 50.***

STABILITY STUDIES:[19]

Stability of a drug has been defined as the ability of a particular formulation, in a specific container, to remain within its physical, chemical, therapeutics and toxicological specifications throughout its shelf life.

Stability testing is used to:

- Provide evidence as to how the quality of the drug product varies with time.
- Establish shelf life for the drug product.
- Determine recommended storage conditions.
- Determine container closure system suitability.

Accelerated stability studies:

Generally the observation of the rate at which the product degrades under normal room temperature requires a long time. The International Conference of Harmonization (ICH) Guidelines titled "Stability testing for new drug substances and product" (Q1A) describes the stability test requirements for drug registration application in the European Union, and United States of America. The accelerated stability was carry out by ICH guidelines. The ICH guideline recommends the following storage conditions for stability studies.

Table No: 29

STORAGE CONDITIONS FOR ACCELERATED STABILITY STUDIES

S.No.	Study	Storage Condition
1.	Long term	25°C±2°C / 60%RH±5%RH
2.	Intermediate	30°C±2°C / 65%RH±5%RH
3.	Accelerated	40°C±2°C / 75%RH±5%RH

As per ICH guidelines, the samples for stability analysis must be exposed to an environment of 40˚C±2˚C / 75% RH±5% RH for a period of 3 months. As per the standard protocol the samples must be analysed at 0, 1, 2, and 3 months time points. Accelerated stability studies were performed for the final enteric coated tablets. The tablets were packed in blister packing material and loaded into the stability chamber under 40±2˚C / 75% ±5% RH and the samples were analyzed at 0, 1, 2 and 3 months time points.

Test Performed:

a. Test for physical parameters (description, hardness, thickness, friability, disintegration).

b. Assay.

c. *In vitro* Dissolution Study.

The results of the stability studies are tabulated in ***Table No: 51 and 52.*** The data was analyzed for any significant change in the values from the initial data.

7. RESULTS AND DISCUSSION

PRE FORMULATION STUDIES:

Evaluation of Active pharmaceutical ingredient (API):

A. Physio - Chemical evaluation:

1. Description:

Table No: 30 Description of bisacodyl

Tests	Specification	Observation
Colour	White to Off-white crystalline powder	White crystalline powder
Odour	Odourless	Odourless

2. Solubility analysis:

Table No: 31 Solubility analysis of bisacodyl

S.No	Solvent	Observation
1.	Water	Insoluble
2.	Acetone	Soluble
3.	Isopropyl alcohol	Sparingly soluble

Inference:

Based on the solubility analysis, It is confirmed that the bisacodyl powder is only soluble in solvents like acetone and isopropyl alcohol whereas it is insoluble in water.

3. Moisture content:

Table No: 32 Moisture content of bisacodyl

S.No	Limits	Observation
1.	NMT 2%	0.96% at 60^0C

Inference:

Based on the observed value, the moisture content of bisacodyl was found to be with in limits as specified

4. Micromeritic properties:

Table No: 33 Micromeritic properties of bisacodyl

API	Bulk density (g/ml)	Tapped density (g/ml)	Compressibility Index (%)	Hausner's ratio	Moisture content (%)
Bisacodyl	0.402±0.0005	0.519± 0.0003	21.49±0.001	1.29±0.0001	0.96%

Inference:

a. The bulk density of the powder was found to be 0.402gm/ml

b. The tapped density of the powder was found to be 0.519gm/ml.

c. The compressibility Index was found to be 21.49% indicating fair flow properties.

d. The hausner's ratio was found to be 1.29 and the observed value indicates that the powder shows moderate flow properties.

e. The moisture content was found to be 0.96% at 60^0C.

Based on the above results, it was concluded that this drug is not suitable for formulating the tablets by direct compression method due to fine particle size and moderate flow in nature.

5. Particle size determination:

Table No: 34 Particle size determination of bisacodyl

Sieve No. (#)	Sieve aperture (µm)	Quantity weight retained (gm)	Cumulative weight retained (gm)	% Retained
20	850 µm	0.35	0.35	2.33
40	425 µm	0.86	1.21	8.055
60	250 µm	3.15	4.36	29.028
100	150 µm	4.25	8.61	57.323
Pan	….	6.35	14.96	99.60

Initial weight of powder = 15.02g

Final weight of powder = 14.96g

Percentage retained =

$$\frac{\text{Powder retained on each sieve}}{\text{Initial weight}} \times 100$$

Percentage retained = 99.60%

Inference:

From the particle size analysis, it is concluded that almost 99.60 % of the drug passes through all sieves. Thus the particle size of the API was found to be moderately coarse powder.

B. DRUG- EXCIPIENT COMPATIBILITY STUDIES:

The following ***Table No:*** **35,** illustrates the drug – excipient compatible studies.

I. Physical compatibility studies:

Table No: 35 Drug - Excipient physical compatibility studies:

S.No	Composition details	Initial	Storage condition / duration	Comments
			(40^0C / 75%RH) / 30days	
1	API (Bisacodyl)	White to off white crystalline powder	NCC	Compatible
2	API+ Dibasic calcium phosphate	Off White crystalline Powder	NCC	Compatible
3	API + Kaolin	Light brown crystalline Powder	NCC	Compatible
4	API + Lactose	Off White crystalline Powder	NCC	Compatible
5	API + Starch	Off White crystalline Powder	NCC	Compatible
6.	API + CCS	White crystalline Powder	NCC	Compatible
7.	API + PVP	Off White crystalline Powder	NCC	Compatible
8.	API + SLS	Off White crystalline Powder	NCC	Compatible

*** NCC- No Characteristic Change**

II. FT-IR compatibility studies:

The FT-IR studies of pure bisacodyl and individual excipients with bisacodyl were carried out to study the interaction between the drug and excipients. The analysed FT-IR spectra and interpretation data for the drug sample and the drug- excipient mixtures were shown in the ***Figure No:7,8,9,10,11,12,13,14 and Table No: 36, 37, 38,39, 40, 41 and 43.***

Figure No: 7

FT-IR spectrum of bisacodyl pure drug

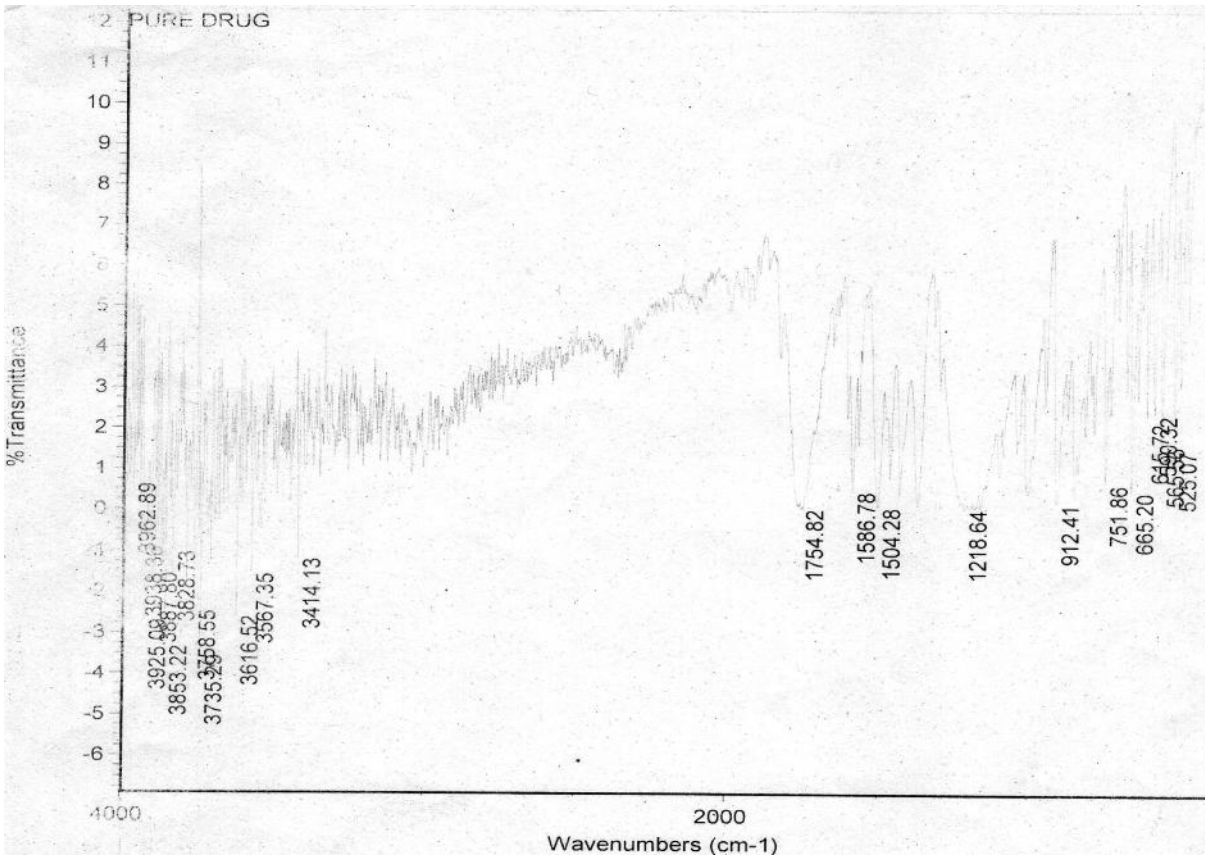


Table No: 36

Interpretation of Bisacodyl Pure Drug

Wave number (cm^{-1})	Signal assignment
1586.78	C-C Stretching
1504.28	-C=C Stretching
1435.00	C-C Aromatic stretching
1370.00	C-H Alkane rocking
1218.64	C-N Aromatics stretching
1010	-C-O Stretching

Figure No: 8

FT-IR spectrum of bisacodyl with dibasic calcium phosphate

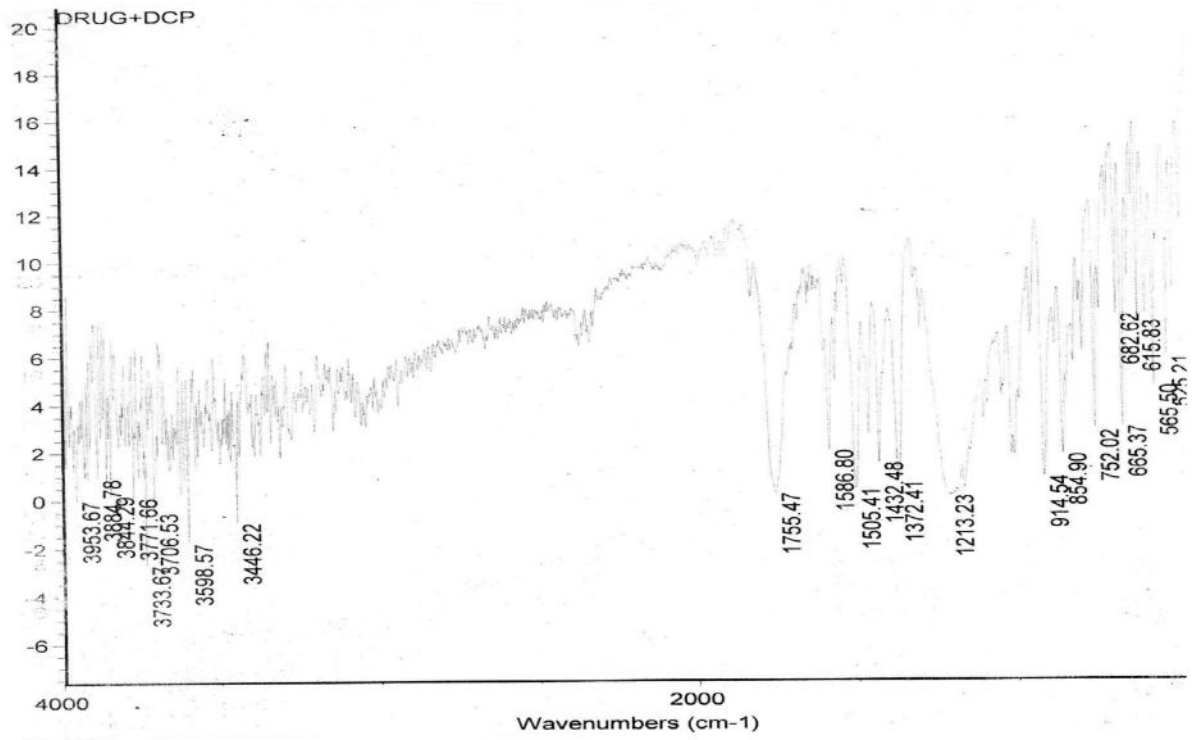


Table No: 37

Interpretation of bisacodyl with dibasic calcium phosphate

Wave number (cm^{-1})	Signal assignment
1755.47	C=O Ester stretching
1372.41	C-H Aldehyde deformation
1586.80	C=C Aromatic stretching
854.90	=C-H Alkene bending
1432.48	C-H Alkane bending
665.37	C-H Wagging
565.50	C-C Skeletal vibration

Figure No: 9

FT-IR spectrum of bisacodyl with kaolin

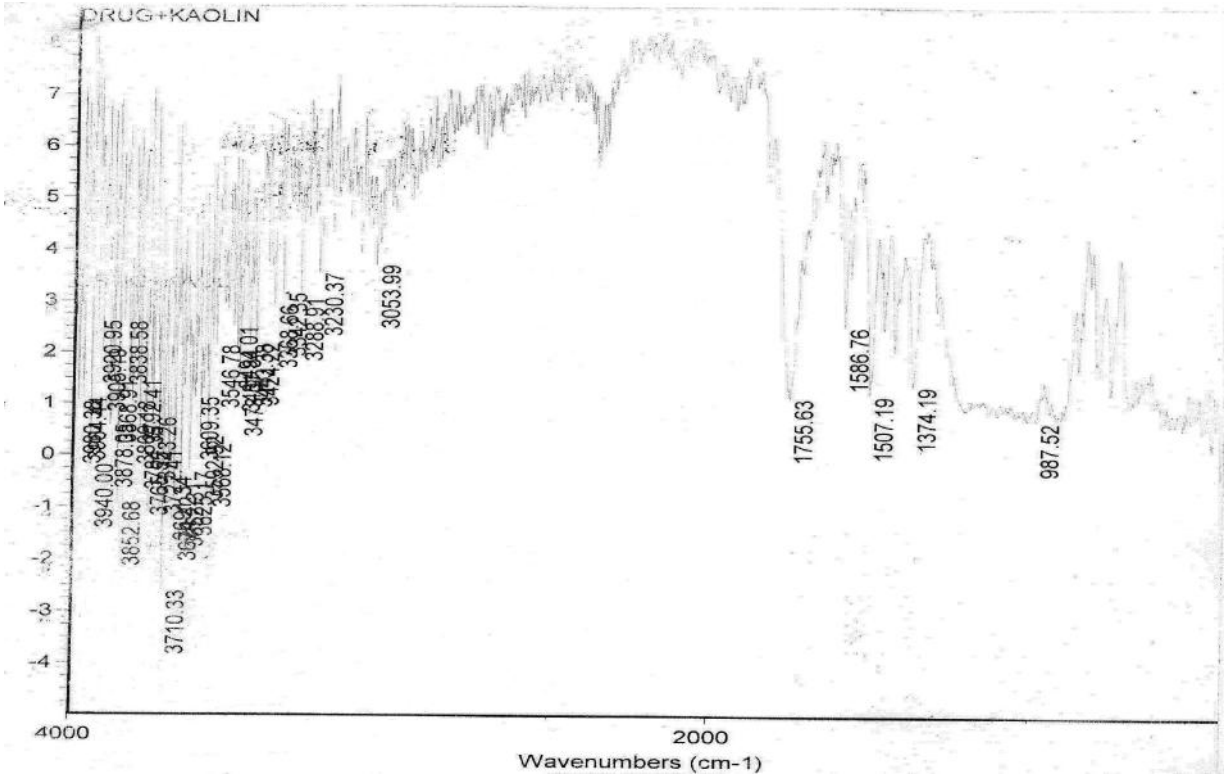


Table No: 38

Interpretation of bisacodyl with kaolin

Wave number (cm^{-1})	Signal assignment
1586.76	C-C Stretching
1507.19	-C=C Alkene stretching
1374.19	C-H Alkane rocking
1213.24	C-N Aromatic stretching
987.52	-C-O Stretching

Figure No: 10

FT-IR spectrum of bisacodyl with lactose

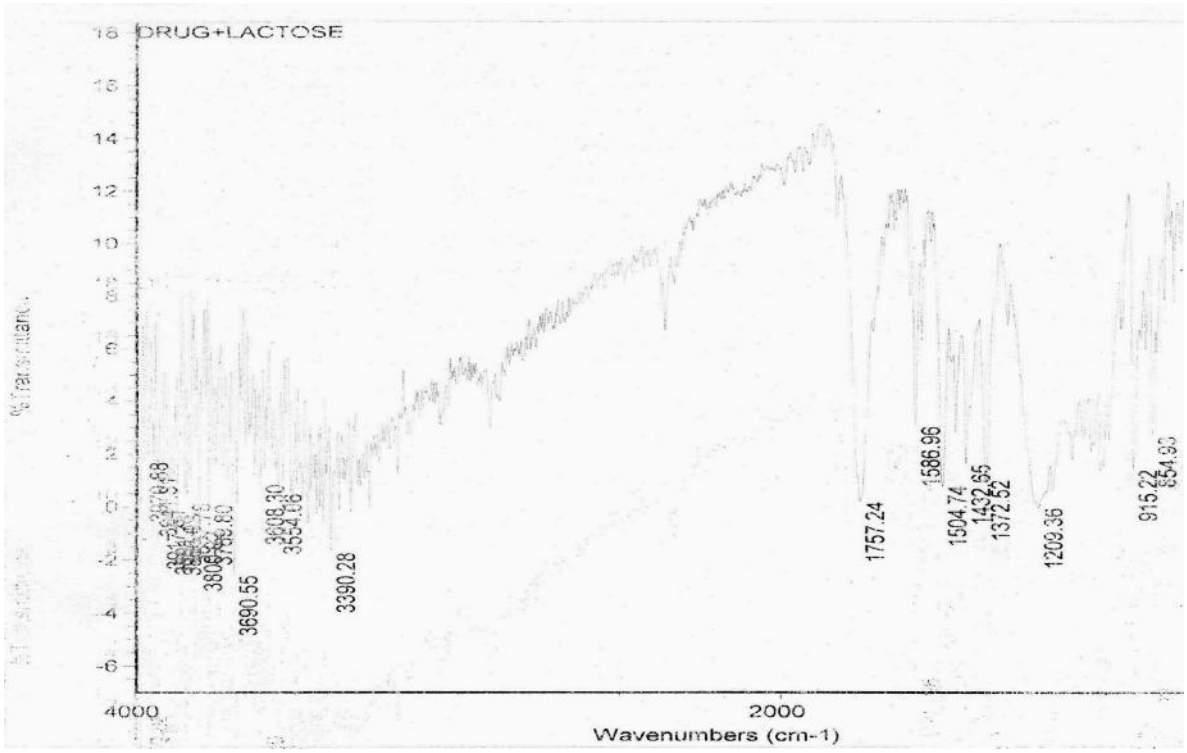


Table No: 39

Interpretation of bisacodyl with lactose

Wave number (cm^{-1})	Signal assignment
1757.24	C=O Carbonyl stretching
3554.06	N-H Amine stretching
3608.30	O-H Stretching
1372.52	C=C Stretching
665.44	C-H Wagging
1586.96	C=C Stretching

Figure No: 11

FT-IR spectrum of bisacodyl with starch

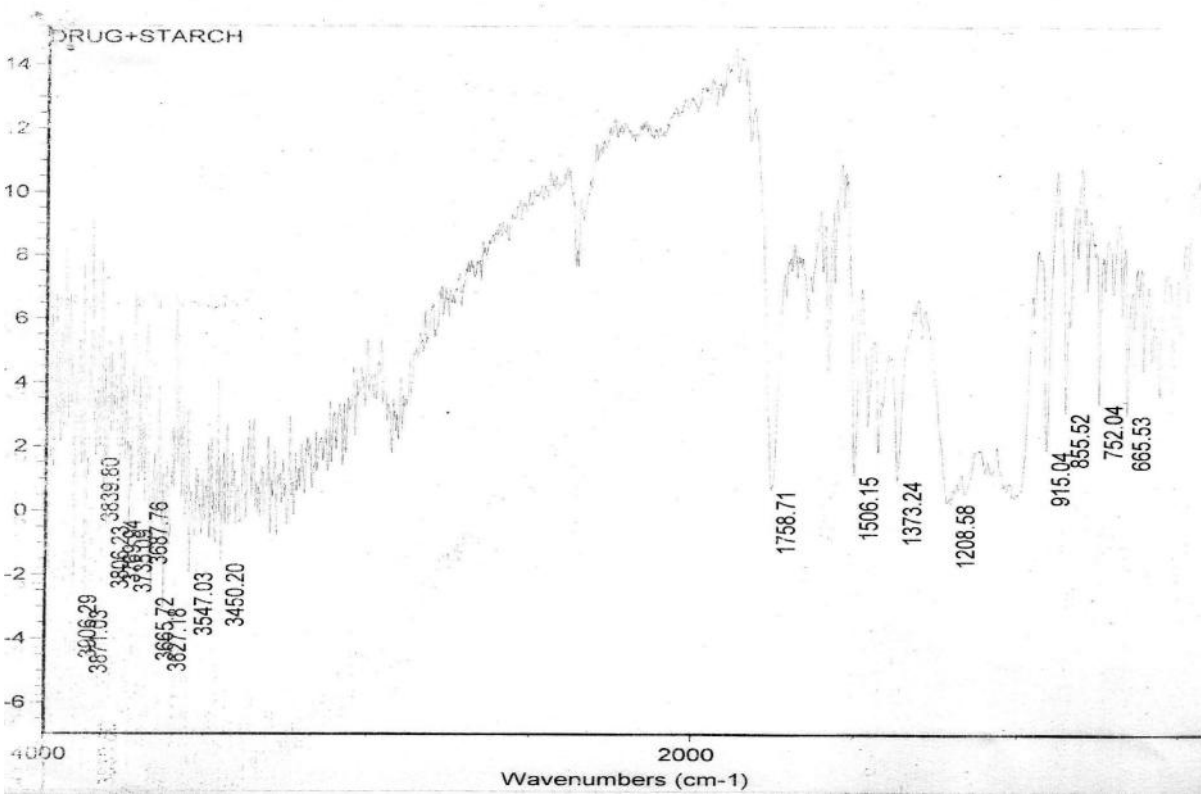


Table No: 40

Interpretation of bisacodyl with starch

Wave number (cm^{-1})	Signal assignment
3665.72	O-H Alcohol free stretching
3450.20	O-H Alcohol broad stretching
1208.58	C-N Amine stretching
1758.71	C=O Stretching
1373.24	C=C Aromatic deformation
915.04	C-O Stretching

Figure No: 12

FT-IR spectrum of bisacodyl with croscarmellose sodium

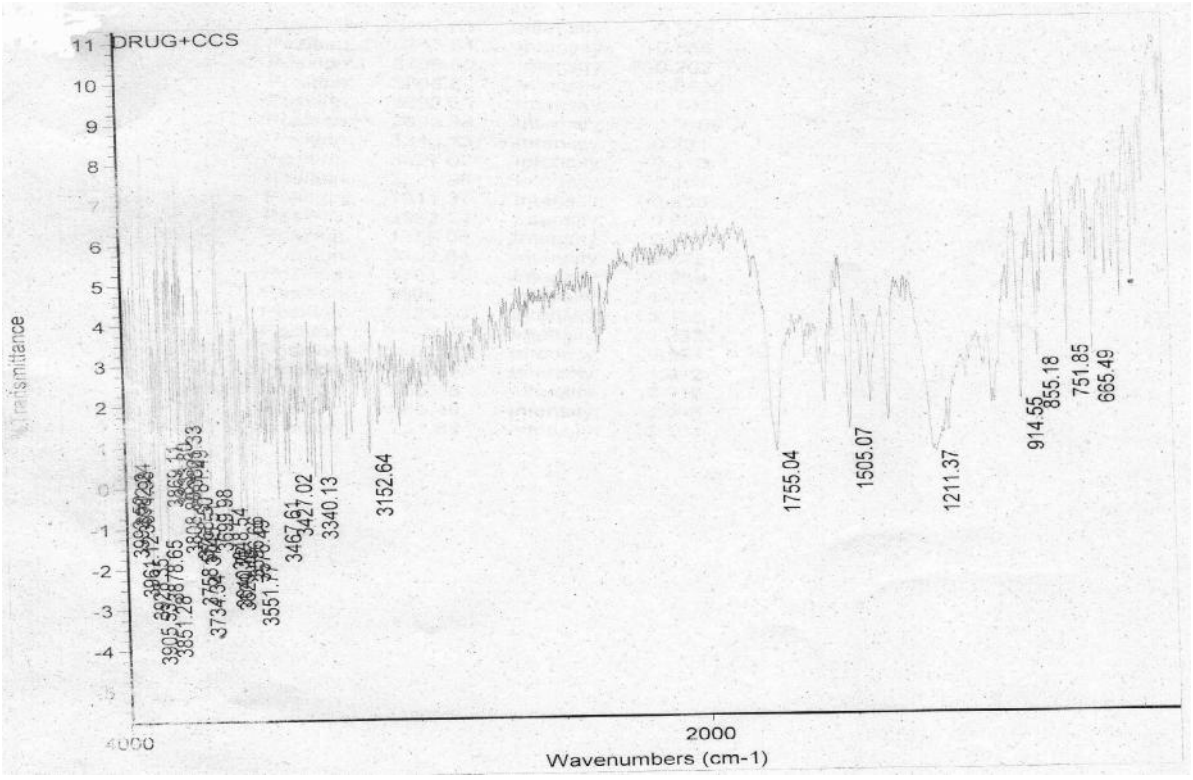


Table No: 41

Interpretation of bisacodyl with croscarmellose sodium

Wave number (cm^{-1})	Signal assignment
1580.00	C-C Stretching
1505.07	-C=C Stretching
1440.00	C-C Aromatic stretching
1370.00	C-H Alkane rocking
1211.37	C-N Aromatic stretching
665.49	C-H Rocking

Figure No: 13

FT-IR spectrum of bisacodyl with polyvinyl pyrrolidione

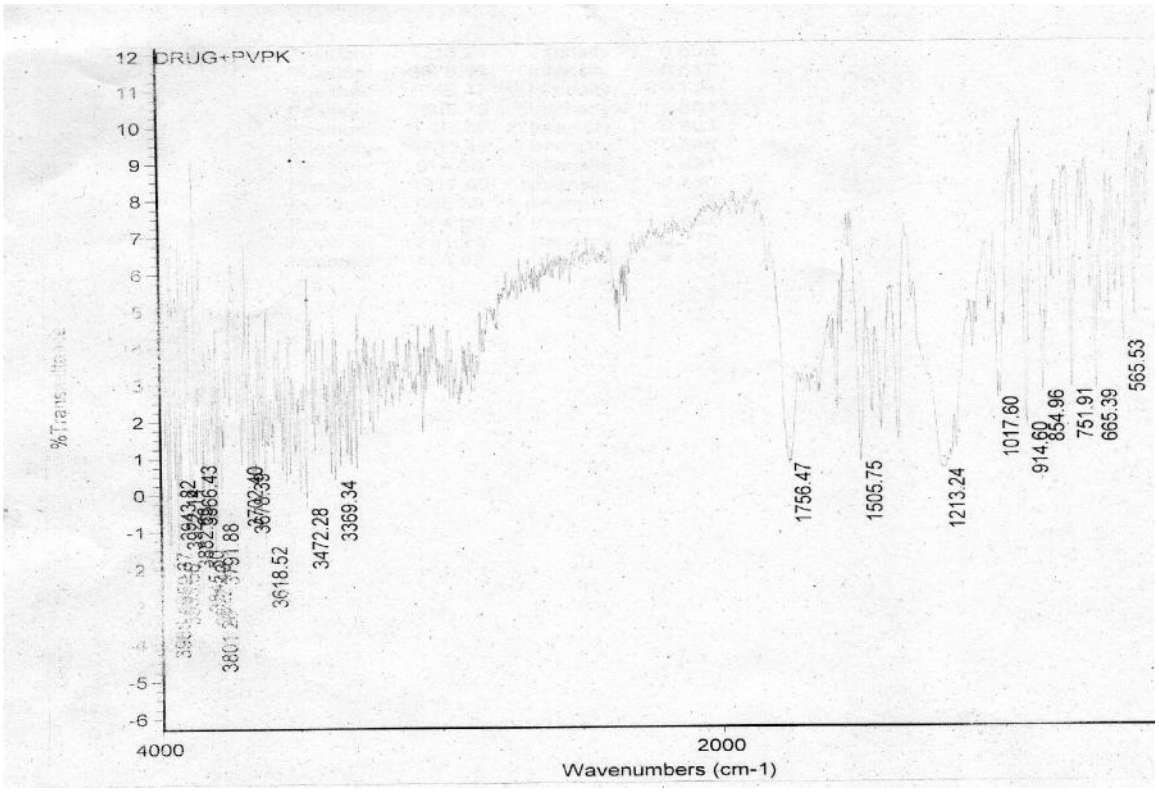


Table No: 42

Interpretation of bisacodyl with polyvinyl pyrrolidione

Wave number (cm^{-1})	Signal assignment
1756.47	C=O Ester stretching
1505.75	-C=C Stretching
1370.00	C-H Alkane rocking
1213.24	C-N Aromatic stretching
1017.6	-C-O Stretching
751.91	Benzene ring stretching

Figure No: 14

FT-IR spectrum of bisacodyl with sodium lauryl sulphate

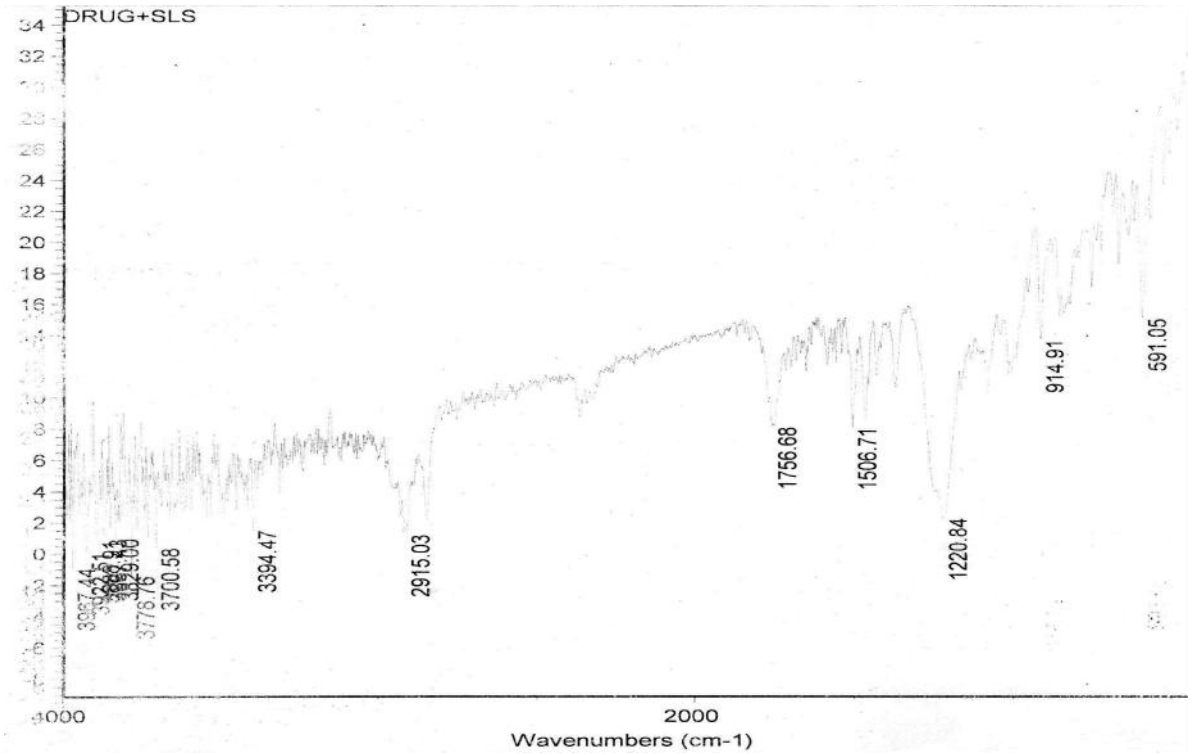


Table No: 43

Interpretation of bisacodyl with sodium lauryl sulphate

Wave number (cm^{-1})	Signal assignment
2915.03	C-H Stretching
3394.47	O-H Alcohol stretching
1220.84	C-H deformation
1756.68	C=O Carbonyl stretching
1506.71	C=C Aromatic stretching

EVALUATION OF PRE COMPRESSION PARAMETERS FOR POWDER BLEND:

The pre compression parameters for the powder blend or granules were evaluated as per procedure mentioned in the methodology part and the results were tabulated in ***Table No: 44 and 45.***

Table No:44

Pre - Compression parameters for powder blend

CODE	Bulk density * (g/ml)	Tapped density * (g/ml)	Compresibility Index * (%)	Hausner's Ratio *	Moisture Content (%)
F1	0.376±0.007	0.430±0.005	12.49±0.007	1.14±0.002	1.58%
F2	0.380±0.001	0.464±0.002	18.14±0.006	1.22±0.001	1.39%
F3	0.382±0.001	0.449±0.004	14.99±0.009	1.17±0.006	1.54%
F4	0.387±0.007	0.471±0.003	17.83±0.004	1.21±0.007	1.66%
F5	0.386±0.002	0.461±0.002	15.70±0.002	1.17±0.007	1.22%
F6	0.378±0.001	0.408±0.006	7.50±0.001	1.08±0.009	1.05%
F7	0.374±0.005	0.394±0.002	4.99±0.007	1.05±0.007	0.92%

***All the values are mean ±SD, n=3**

Table No: 45

Sieve analysis for the powder blends of formulations (F1 – F7)

Sieve No. (#)	Sieve aperture (µm)	% Retained						
		F1	F2	F3	F4	F5	F6	F7
20	850	2.39	1.27	0.69	2.19	0.39	3.18	1.58
40	425	17.80	10.23	7.70	12.98	8.71	21.11	8.98
60	250	43.15	20.51	26.46	39.95	24.18	40.83	23.75
100	150	77.68	65.61	58.20	76.90	51.07	83.86	55.88
Pan	….	96.00	99.28	98.72	99.36	98.64	99.60	99.50

Inference:

The result of flow properties of prepared granules of various formulations of bisacodyl were given in the ***Table No: 44 and 45.*** Flow properties of the granules, resistance to particle movement can be judged from the bulk density, tapped density, compressibility index, hausner's ratio. This measurement gives qualitative and quantitative assessment of internal cohesive and frictional force under low levels of external loading as might be applied in mixing and tableting. The bulk density was found within the range of 0.374 to 0.382 g/ml. The tapped density was found within the range of 0.394 to 0.471 g/ml. using the density data, hausner's ratio and compressibility index was calculated. The hausner's ratio was found within the ranges of 1.05 to 1.22 which indicates better flowability. The Compressibility index was found within the ranges of 4.99 to 18.14% , indicating good flow properties.

EVALUATION OF POST COMPRESSION PARAMETERS FOR COMPRESSED TABLETS:

The post compression parameters were evaluated for the core and enteric- coated tablets and the results were tabulated in ***Table No: 46 and 47*.**

Table No: 46

Evaluation of post- compression parameters for core tablets

CODE	General appearance	Weight variation (mg)	Thickness* (mm)	Friability* (%)	Hardness* (kg/cm^2)	Disintegration Time # (minutes)
F1	Round, Convex	120±0.5	2.87±0.01	0.28±0.09	7.0±0.2	7min 45sec ±0.011
F2	Round, Convex	120±0.5	2.95±0.02	0.35±0.02	6.5±0.1	8min10sec ±0.056
F3	Round, Convex	100±0.6	3.02±0.10	1.32±0.03	6.0±0.2	7min 15sec ±0.018
F4	Round, Convex	100±0.3	3.00± 0.08	0.19±0.04	5.3±0.3	6min 10sec ±0.052
F5	Round, Convex	100±0.2	3.09±0.03	0.24±0.05	6.5±0.3	9min 50sec ±0.031
F6	Round, Convex	100±0.9	3.10±0.04	0.15±0.02	4.0±0.8	5min 10sec ±0.045
F7	Round, Convex	100±0.1	3.20±0.05	0.10±0.01	3.0±0.2	2min 17sec ±0.021

***All the values are mean ±SD, n=3**

#All the values are mean ±SD, n=6

Figure No: 15

Profile of hardness for various formulations (F1- F7)

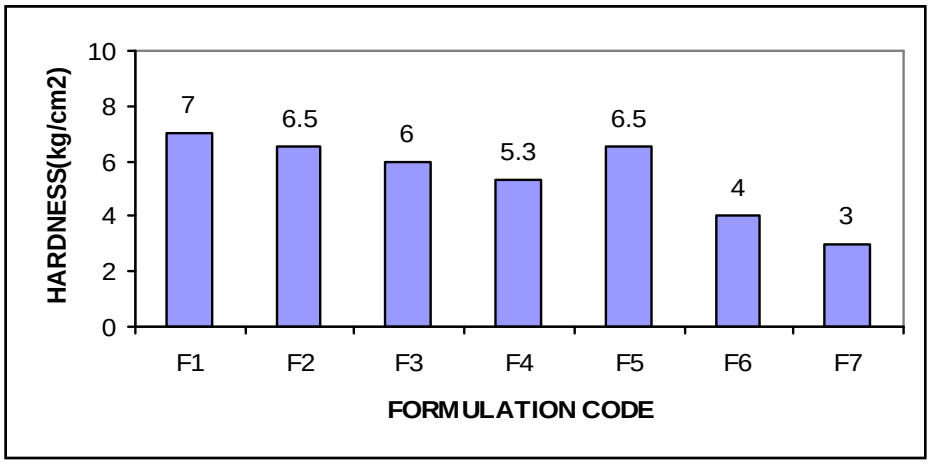


Figure No: 16

Profile of friability for various formulations (F1- F7)

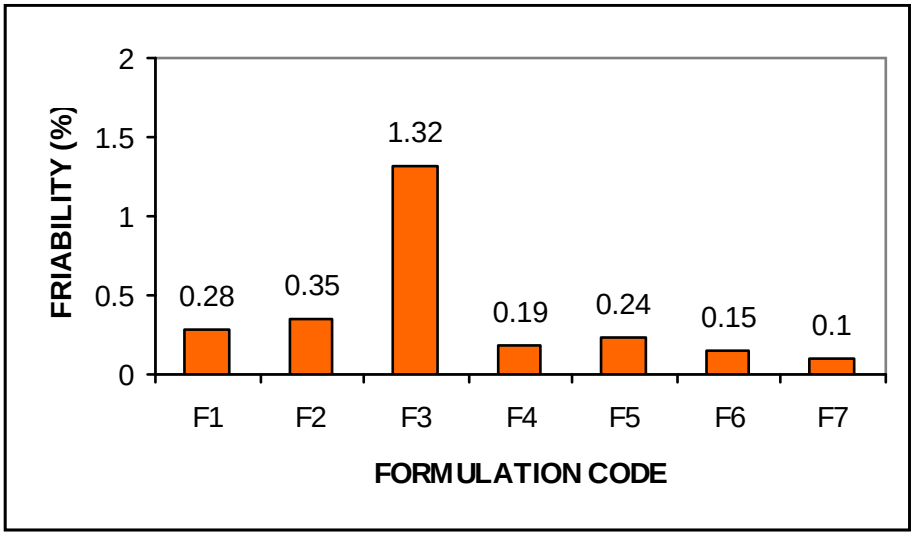


Figure No: 17

Profile of Thickness for various formulations (F1- F7)

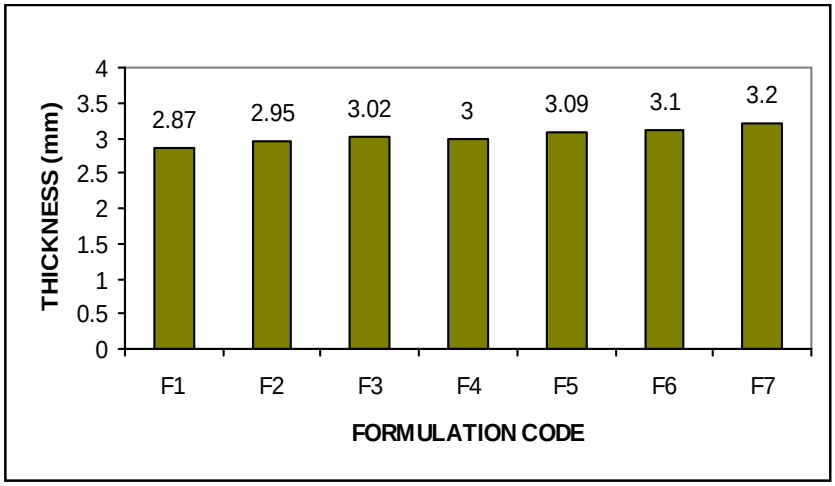


Table No: 47

***Invitro d*issolution data for the core tablets in pH-7.4 buffer medium at 45mins**

Time	F1	F2	F3	F4	F5	F6	F7
45 mins	74.25%	79.20%	83.30%	85.95%	80.10%	89.62%	93.98%

Tolerances:

Not less than 70% of the labelled amount of bisacodyl dissolved in 45 minutes

Figure No: 18

***Invitro* Dissolution profile of core tablets for various formulations (F1- F7)**

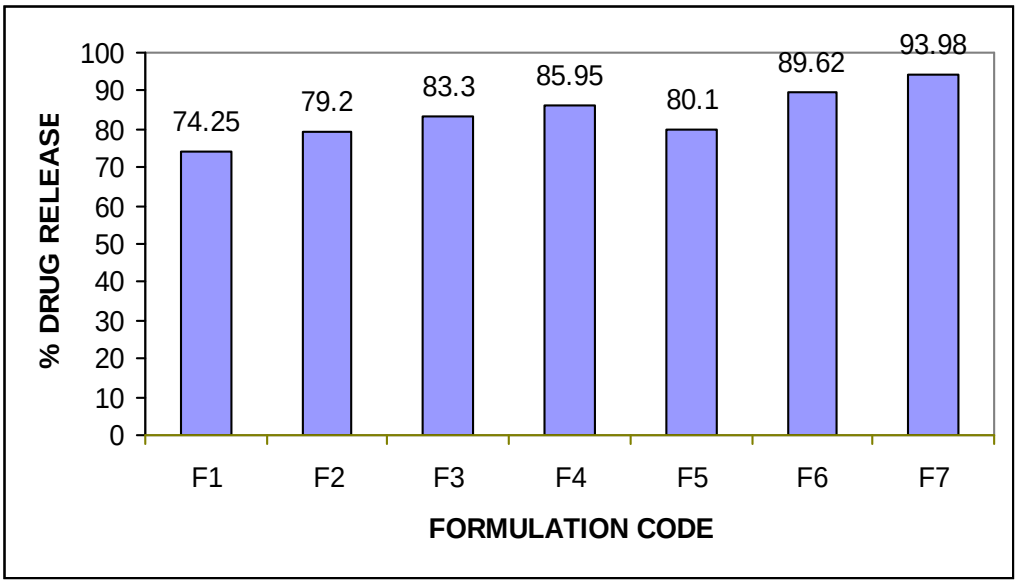


Table No: 48

Evaluation of post-compression parameters for enteric coated tablets

Code	Average Weight* (mg)	Thickness (mm)*	Hardness* (Kg/cm^2)	Disintegration Time # (minutes)	Assay (%)*
F7	109.15±0.04	3.14±0.03	4.0±0.1	6min23sec ± 0.02	99.92 ± 0.08

***All the values are mean ±SD, n=3**

#All the values are mean ±SD, n=6

Table No: 49

***Invitro* dissolution profile for the innovator product and formulation (F7)**

Dissolution medium	Sampling time	% Drug release	
		Innovator	F7
Simulated gastric fluid (0.1N HCL)	120 minutes	0.276%	0.055%
Simulated intestinal fluid (pH 7.4 phosphate buffer)	45 minutes	87.37%	90.74%

Limits:

- The amount of bisacodyl released in case of simulated gastric fluid (0.1 N HCL) is Not More Than 5% of the stated amount.
- The amount of bisacodyl released in case of simulated intestinal fluid (pH 7.4) is Not Less Than 75% (Q) of the stated amount.

Comparative *Invitro* dissolution study using similarity factor:

Table No: 50

***Invitro* dissolution profile comparison using similarity factor for the innovator product with the sample (F7)**

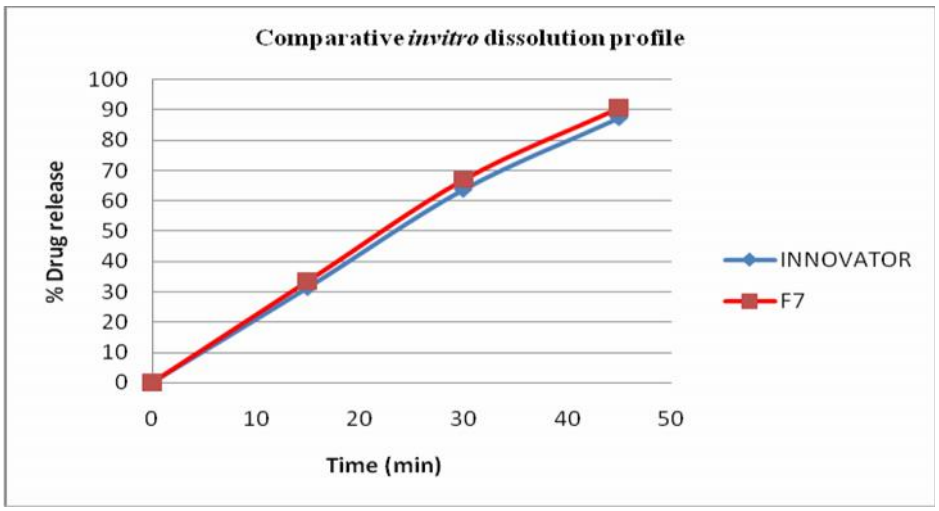
Time (mins)	Reference(R)	Test (T)	$R_T - T_T$	$(R_T - T_T)^2$	$\lvert R_T - T_T \rvert$
0	0.00	0.00	0.00	0.00	0.00
15	31.37	33.55	- 2.18	4.752	2.18
30	63.73	67.03	-3.3	10.890	3.3
45	87.37	90.74	-3.37	11.356	3.37

Inference:

On substituting the observed values in the appropriate formula, the difference factor(f_1) and the similarity factor(f_2) was found to be 5.32 and 75.08.

Figure No: 19

Comparative *Invitro* dissolution profile for the innovator with formulation (F7)



ASSAY:

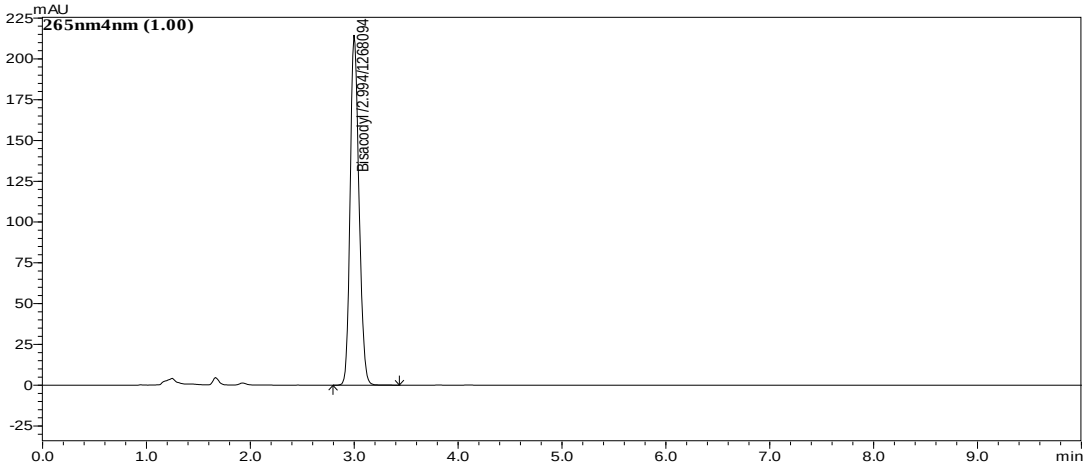
The assay determination for the blank, standard and sample was carried out by the HPLC method.

Standard chromatogram of bisacodyl:

The peak area plot of bisacodyl standard chromatogram is given in the ***figure no:20.***

Figure No: 20

Standard chromatogram of Bisacodyl



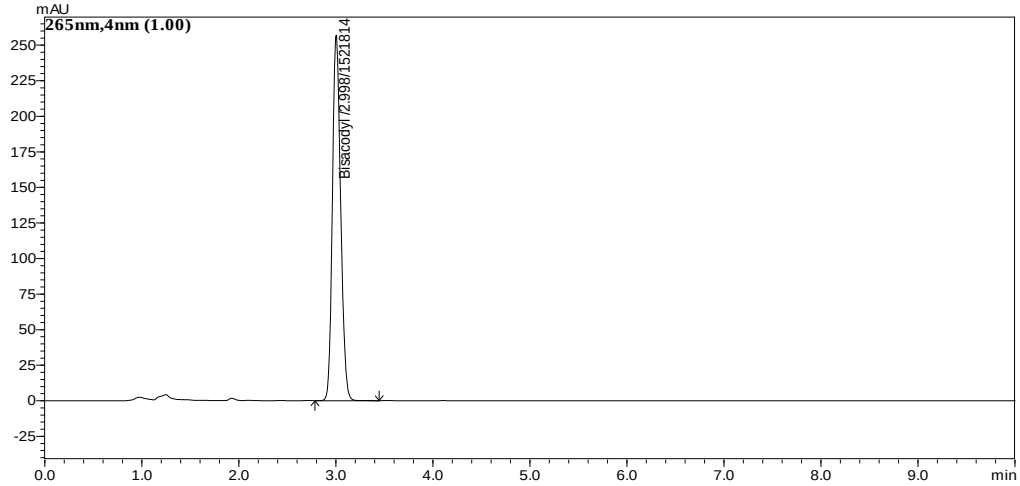
Name	Retention time	Area	Tailing factor	Theoretical Plate
Bisacodyl	2.9	1268094	1.24	4643.3

Sample Chromatogram:

The peak area plot of sample chromatogram is given in the ***figure no:21.***

Figure No: 21

Sample chromatogram



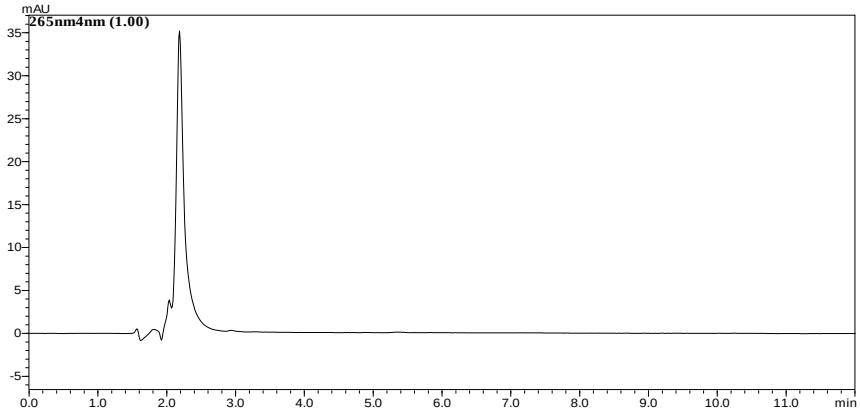
Name	Retention time	Area	Tailing factor	Theoretical Plate
Bisacodyl	2.9	1521814	1.23	4709.6

Blank chromatogram:

The peak area plot of bisacodyl blank chromatogram is given in the ***figure no:22.***

Figure No:22

Blank chromatogram



STABILITY STUDIES:

Table No: 51

Accelerated stability data of physical parameters for the formulation (F7)

Physical parameters	Storage conditions			
	40˚C±2˚C / 75% RH±5% RH			
	Initial	1st month	2nd month	3rd month
Description	Pale yellow, round enteric coated tablet	Pale yellow, round enteric coated tablet	Pale yellow, round enteric coated tablet	Pale yellow, round enteric coated tablet
Avg.weight* (mg)	109.15±0.04	109.21±0.02	109.55±0.04	109.89±0.01
Hardness* (kg/cm^2)	4.0±0.1	3.8±0.2	4.2±0.1	3.5±0.15
Thickness* (mm)	3.14±0.03	3.14±0.08	3.15±0.01	3.14±0.05
Disintegration time	6min23sec ± 0.02	6min 40sec ± 0.02	7min 10sec ± 0.05	6min 89sec ± 0.07

***All the values are mean ±SD, n=3**

Table No: 52

Accelerated stability data of *Invitro* dissolution and assay for the formulation (F7)

Parameters	Specifications	Storage conditions			
		40˚C±2˚C / 75% RH±5% RH			
		Initial	1st month	2nd month	3rd month
Simulated gastric fluid (0.1N HCL)	NMT 5% in 120minutes	0.055%	0.063%	0.087%	0.109%
Simulated intestinal fluid (pH 7.4 phosphate buffer)	NLT 75% in 45 minutes	90.74%	89.95%	89.18%	88.69%
Assay (%)	95.0 to 105.0%	99.92%	99.54%	98.61%	89.87%

Inference:

The formulation (F7) of enteric coated tablets were carried out for the accelerated stability studies for 3 months at 40˚C±2˚C / 75% RH±5% RH in the stability chamber. The resulted data's are given in the ***Table No: 51 and 52.*** The results reveals that no significant changes in the physical parameters at the end of 1st, 2nd,3rd month. The drug content and *in vitro* dissolution profile are remained with out any significant changes, at the end of 1st, 2nd, 3rd month. Hence it is concluded that the formulated enteric coated tablets are stable and the data obtained could be used to predict the shelf life of the product.

DISCUSSION

The present aim of the work is to develop and formulate the stable bisacodyl enteric coated tablets and to comply the *invitro* dissolution parameters with the innovator product.

As per British pharmacopoeial specifications (BP 2013), the bisacodyl tablets should comply the *invitro* dissolution test as prescribed in the monograph. As per specifications, amount of bisacodyl released in the dissolution medium is Not More Than 5% in case of acid medium and Not Less Than 75% (Q) of the stated amount in case of pH 7.4 phosphate buffer medium.

Since bisacodyl is an highly acid liable drug, it is necessary to formulate the tablet as enteric coated tablets which resists the drug releasing in the stomach.

In this work, all the core tablets were formulated by wet granulation method by using povidone as binder. Aqueous coating is performed for the both seal and enteric coating process.

The present work was initiated with the preformulation studies for the API and evaluating the parameters like description, solubility analysis, moisture content, micromeritic properties and particle size determination. The evaluating in-process parameters for the powder blend are bulk density, tapped density, compressibility index, moisture content and hausner's ratio. The compressed tablets were evaluated for the parameters like thickness, hardness, friability, assay and *invitro* dissolution study.

The impacts observed from the various in-process parameters for the powder blends and compressed tablets were discussed one by one below.

PRE FORMULATION STUDIES:

Evaluation of Active Pharmaceutical Ingredient (API):

The preformulation studies for the API reveals that the description of the bisacodyl powder was appeared as white crystalline and has no odour. Based on the solubility analysis, the API was found to be insoluble in water where as soluble in acetone and isopropyl alcohol . The moisture content was found to be 0.96% at 60^0C. The micromeritic properties of API was found to be satisfactory and it shows an moderate flow properties. The particle size determination was performed by sieving method. It shows that almost 99.60% of the drug

passes through all the sieves and it is an moderately coarse powder. From the drug- excipients compatibility study, it was observed that there was no significant change or interaction between drug and excipients on storage conditions at 40^0C / 75%RH for 2 weeks.

EVALUATION PARAMETERS:

I. Evaluation of Pre Compression parameters for Powder Blend:

The results of evaluation of powder blends for all the formulations (F1 to F7) were given in the ***Table No:44 and 45***, it suggests that it has good flow property. The bulk density values observed from the formulations F1 to F7 was found to be within the range 0.374 to 0.387g/ml. The formulation F7 shows lowest value when compared to other formulations. The tapped density values observed from the formulations F1 to F7 was found to be with in range 0.374 to 0.464g/ml. Settling down of granules for F1 to F5 is difficult when tapping whereas F6 and F7 formulation is not difficult. The compressibility index for the formulations F1 to F5 was found to be with in range 12.49 to 18.14 % which shows fair flow in granules whereas formulation F6 and F7 shows good flow characters when compared to other five formulations. The hausner's ratio for the formulations F1 to F7 was found within the range 1.05 to 1.22. From the observed values the flow type was good for all formulations.

II. Evaluation of Post Compression parameters for core tablets :

The results of compressed core tablets were given in the ***Table No*:*46 and 47*** All the formulation batches of core tablets shows good in appearance.

In the formulation F1, with the presence of diluents- kaolin(10.83%) , lactose anhydrous(40.83%) were added in intra and extra granular part , starch(26.6%), and povidone (2.5%), it shows that hardness of tablets was found to be 7.0 (kg/cm^2) and drug release is only 74.25% in the buffer medium. Due to low drug release initially, if coated this will tends to decrease more and fails the limits. So the next trial is taken with the improvement in solubility.

In the formulation F2, with the incorporation of dibasic calcium phosphate (8.33%) and slightly increasing the percentage concentration of kaolin and starch, removing the lactose anhydrous from extra granular part, the hardness of tablets shows 6.5 (kg/cm^2) only an slight difference and drug release was found to be 79.20% in the buffer medium.

In the formulation F3, inclusion of 1% sodium lauryl sulphate as wetting agent and lactose anhydrous (27%) and povidone (3%) where friability failed in this batch.

In the formulation F4, removing sodium lauryl sulphate and starch were removed, instead micro crystalline cellulose (20%), DCP (19%) and kaolin (25%)were added. The disintegration time was found to be 6mins 10sec, an little faster when compared to other three trials. In this trial, tablets friability have passed. The drug release was found to be better when compared with previous batches (85.95%). In this trial, lot of materials sticked to the meshes it may be due to kaolin at increasing concentration.

In the formulation F5, lactose is removed and starch (20%), micro crystalline cellulose (27%), Dibasic calcium phosphate (19%) and Kaolin(18%) were added, disintegration time was found to be 9mins 50sec and drug release also reduced to 80.10% when compared to previous trial. Since harder tablet is formed in this trial, further trial is taken to reduce the hardness.

In the formulation F6, sodium lauryl sulphate at 0.3% concentration and lactose (27%) were incorporated and micro crystalline cellulose is removed where the tablets disintegration time was found to be 5min 10sec, an little improvement and the drug release was found to be 89.62%. Trial 6 show better dissolution in pH 7.4 buffer medium, hence keeping 'F6' as base formula further trial is taken.

In the formulation F7, The tablet shows good mechanical strength and the disintegrating time was found to be 2min 17sec. The drug release was found to be 93.98% in pH7.4 phosphate buffer medium.

In all the formulations from F1 to F7, croscarmellose sodium were used as the disintegrant and povidone K-30 used as an binder.

Based on disintegration time and drug release values observed for the various formulations, F7 shows good disintegration time and drug release in the buffer medium.

F7 formulation core tablet shows satisfactory analytical results and hence decided to enteric coat the core tablet with 2% seal coating and 7% enteric coating with the poly methacryllic acid methyl acrylate as polymer.

III. Evaluation of Post-compression Parameters for Enteric Coated Tablet:

The optmized formulation (F7) were subjected to coating with 2% seal coating with the hydroxypropyl methyl cellulose 15-cps as polymer and 7 % enteric- coating with the poly methacryllic acid methyl acrylate as polymer. The results for the evaluated parameters were given in the ***Table No: 48 and 49***. The thickness of the tablet was found to be 3.14mm and hardness is 4.0 kg/cm^2. The % drug content was found to be 99.92% which is acceptable under the limits. The % drug release was found to be 0.055% in the acid medium and 90.74% in the buffer medium which is acceptable limits as per monograph.

IV. Comparative *Invitro* dissolution study:

The *Invitro* dissolution profile of formulation (F7) and the innovator product were compared by calculating the differential factor (f1) and similarity factor (f2). The results were tabulated in ***Table No: 50***, and the factors f1 and f2 was found to be 5.32 and 75.08, respectively which is an acceptable limits. Hence the two products were considered as similar and comparable.

V. Stability studies:

Accelerated stability studies were carried out for the optimized formulation (F7) enteric coated tablets. 20 tablets were packed in blister packing and loaded in the stability chamber for 3 months at 40˚C±2˚C / 75% RH±5% RH. The resulted data's are given in the ***Table No:51 and 52.*** No significant changes was observed in the physical parameters, drug release and drug content when stored at 40˚C±2˚C / 75% RH±5% RH for 3 months. The drug release was found to be 88.68% in the buffer medium and the drug content is 89.87% were satisfies the pharmacopoeial limits. Hence it is concluded that the formulated enteric coated tablets were stable.

8. CONCLUSION

The present study involves to design and formulate the enteric - coated tablets of bisacodyl and to comply the *invitro* dissolution data as per BP specifications.

Preformulation studies has been performed to study the nature of API and compatibility of API with excipients by physical observation and FT-IR studies. The results showed that there was no interaction between API and all the excipients selected.

Enteric coated tablets of bisacodyl were successfully formulated by wet granulation method using the selected excipient with required quantities. The formulated tablets were evaluated for both pre-compression and post-compression parameters like bulk density, tapped density, compressibility index, hausner's ratio, moisture content, hardness, thickness, disintegration time and *invitro* dissolution and assay as per requirements of standards. The results were found to be satisfactory with the pharmacopoeial specifications.

Among all the entire batches, formulation (F7) is the best formulation which complies all the pharmacopoeial specifications. The best formulation is selected based on the *invitro* dissolution data when compared with that of innovator product using the similarity factor.

The most satisfactory formulation has been subjected to Accelerated stability studies as per ICH guidelines for 3 months at 40˚C±2˚C / 75% ±5% RH. The results of stability studies shows no significant changes in the physical parameters of the tablets, drug content and *invitro* dissolution data until the end of 3 months from the initial values. Hence it is concluded that the formulated bisacodyl enteric coated tablets were stable and this study fulfilled all the pharamcopoeial specifications.

Future study:

The present work may explore the following aspects in the future, which may become a valuable assets in the field of pharmaceutical science.

1. Accelerated stability study is continued for another 3months and shelf life is determined.
2. Scale up activity of the optimized formulation.
3. The *invitro* studies can be extended to *invivo* studies by leading to a final conclusion of a successful formulation which can be marketed there after.

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